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OSTEOPOROSIS

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THIS DISCUSSION CONCERNS a 65-year-old man who merely stubs his toe on a table-leg and suffers a fracture of the neck of the femur; a 53-year-old woman who, five years after the menopause, suffers severe back pain and notices that she is inches shorter than she was a few years before. These patients may be suffering from a disease of generalized bone deficiency called osteoporosis. This disease is not localized to one bone; it is a metabolic disorder which may involve the whole skeleton.

In the past, whenever an X-ray of bone showed a deficiency of substance—a decreased density—the condition was labelled osteoporosis, or osteomalacia, or decalcification, or rarefaction. These terms were used almost interchangeably although there was no agreement regarding their meaning. In recent years, largely due to the work of Albright, Reifenstein and their associates, it has become more widely recognized that bone may lose substance and strength for a variety of reasons. In order to understand these reasons, it is important to consider briefly the factors that maintain a normal state in bone.

PHYSIOLOGY OF BONE

Bone is a tissue with organic and inorganic constituents. The organic matrix is composed of cells and their intercellular substance. To this framework is added an inorganic mineral complex. We have only to be reminded of the rapidity of loss of bone substance on immobilization, or of the vigorous growth of callus following a fracture, to be convinced that bone is a living tissue. Growth does not cease with fusion of the epiphyseal plates. On every trabeculum new bone is constantly being manufactured and old bone resorbed. The days of the osteocyte are as numbered as are those of the red blood cell.

For this constantly changing tissue there must be a source of entry for nutrients and an avenue of exit for metabolites. Anatomically, therefore, we may consider the immediate environment, the blood; a source of entry, the gastrointestinal system; and two avenues of exit, the gastrointestinal system and the kidney. We may therefore consider a *primary equilibrium* involving bone, blood, bowel and kidney. The nutrients are chiefly proteins (for the organic matrix), and calcium and phosphorus (for the mineral complex). Changes in blood, bowel or kidney, by affecting the transfer of these nutrients, may result in bone disease.

In addition there are factors which may act at any site in the equilibrium to change bone:

1) Mechanical stimuli—the stresses and strains acting on bone itself.
2) Dietary factors—mainly Vitamin D.
3) Endocrine influences—chiefly the parathyriods, anterior pituitary, thyroid, sex glands and adrenal cortex.

It is therefore important to maintain a dynamic view of bone, and to remember that:

1) The deposition of bone involves two distinct processes; first, the production of an organic matrix, and secondly, the calcification of that matrix.
2) Bone deposition and bone resorption are constantly occurring in health and disease.
3) Generalized bone deficiency is due to an imbalance between bone deposition and bone resorption.

CLASSIFICATION OF GENERALIZED BONE DEFICIENCY

Albright's new concept of generalized bone deficiency is becoming widely recognized. He classifies "too little bone" as follows:

1) Deficient deposition of bone.
   a) Inadequate production of organic bone matrix — osteoporosis.
   b) Failure of calcification of adequate matrix—osteomalacia.
2) Excessive resorption of bone—hyperparathyroidism.

Hyperparathyroidism and osteomalacia will now be briefly discussed in order to clarify this concept of osteoporosis.

HYPERPARATHYROIDISM—EXCESSIVE RESORPTION

Generalized bone deficiency due to excessive resorption of both calcium and organic bone matrix is rare, but is most clearly seen in hyperparathyroidism. Bone throughout the body undergoes loss of substance with varying degrees of cyst formation, deformity and fractures. The mechanism of bone resorption is not completely understood. Parathormone may act directly on bone, but there is considerable evidence to suggest that it acts primarily on the kidney tubules to increase the excretion of phosphates. This results in a fall in serum phosphates. In order to maintain the serum calcium-phosphate-ion-product, the serum calcium is raised by withdrawal of calcium from bone. The elevated serum calcium results in a tendency to metastatic calcification, and an increased urinary excretion of calcium with the danger of calcium deposits in the kidney tubules. When the parathyroid tumor is removed, calcium is no longer drawn from bone and there is a dramatic return to normal.

OSTEOMALACIA—INADEQUATE CALCIFICATION

In osteomalacia (or rickets) bone deficiency is caused by insufficient deposition of mineral nutrients. Histologically there is a wide seam of organic matrix starved of mineral. The calcium-phosphate-ion-product tends to be lower than normal. Osteomalacia may be caused by an inadequate intake of calcium and phosphorus; by inadequate absorption of these minerals from the intestine (as occurs in Vitamin D deficiency and steatorrhea); or by excessive excretion of calcium in the urine

(as occurs in tubular insufficiency, Franconi syndrome, and idiopathic hypercalcuria). Osteomalacia is therefore a disease of mineral metabolism. As far as bone is concerned, the healthy organic matrix readily accepts minerals when these are made available to it. With adequate calcium, phosphorus and Vitamin D therapy, bone is recalcified and the condition corrected.

OSTEOPOROSIS—INADEQUATE MATRIX

In osteoporosis, the parathyroids are normal; the mineral intake (except in malnutrition) is usually considered adequate; serum calcium and phosphorus levels and the urinary excretion of calcium and phosphorus are normal; the serum alkaline phosphatase is usually normal; by increasing the intake of calcium, phosphorus and Vitamin D, no measurable change in bone results. This is to be expected since histologically there is normal calcification of the matrix. The little organic matrix that is present is fully calcified—but there is not enough matrix. Osteoporosis would therefore appear to be a bone deficiency caused by the inadequate formation of organic bone matrix. It is on the basis of these facts that Albright separates osteoporosis from osteomalacia and hyperparathyroidism.

ETIOLOGY OF OSTEOPOROSIS

The cause of this inadequacy of organic bone matrix is at present unknown. Bone lesions resembling osteoporosis have been experimentally produced by starving dogs or by eliminating Vitamin C from the diet, but there is no suggestion of Vitamin C deficiency in most patients suffering from osteoporosis. Since osteoporosis may be associated with such a variety of seemingly unrelated conditions, the issue is further confused. It may occur with malnutrition, hyperthyriodism, acromegaly, diabetes mellitus and Cushing's syndrome. It may follow any acute non-specific stress ("Alarm Reaction" of Selye). Most commonly however, it occurs as senile or postmenopausal osteoporosis in an otherwise healthy person. The disuse atrophy of bone in a paralyzed or immobilized limb is not osteoporosis as here defined since it is a *localized* atrophy of bone.

Lack of exercise, vascular disease and anemia were early suggested as causes of osteoporosis. Muelengracht believed osteoporosis was the result of long-continued calcium deprivation. Unless one imagines chronic calcium lack somehow resulting in diminished production of organic bone matrix, it is difficult to see the relationship of calcium deficiency to osteoporosis.

More recently attention has been focused on the metabolism of the organic bone matrix as the primary site of the disturbance. In malnutrition and hyperthyroidism a deficiency of protein building blocks for the matrix is considered the likely cause.

The possibility of an endocrine imbalance has encouraged investigation of the effects of hormones on bone metabolism. It has been found that androgens and estrogens stimulate bone deposition in some animals and probably in man as well. The androgenic hormones of the adrenal cortex are also anabolic for bone. Antagonistic to the sex hormones and androgenic corticoids are the glucocorticoids of the adrenal cortex which favour catabolism of the organic matrix. It is generally considered

that postmenopausal osteoporosis is due to a deficiency of anabolic sex hormones. Certainly some of the most acute cases of osteoporosis accompany the "artificial menopause" which follows bilateral oophorectomy. Most investigators agree that the osteoporosis occurring in Cushing's syndrome is due to an excess of glucocorticoids. Albright has suggested that a relative excess of glucocorticoids may be responsible for senile osteoporosis. He presents considerable evidence suggesting a decline in androgenic secretions of the adrenal cortex in old age, which he terms "the adrenopause." The menopause, he postulates, followed by "the adrenopause," would leave the catabolic glucocorticoids unopposed and result in osteoporosis. Selye has suggested that the acute osteoporosis which accompanies non-specific stress may be due to an excess of glucocorticoids. The elevated 11-oxysteroid urinary exretions observed in these cases tend to support this belief. The logical attempt to counteract the predominance of these catabolic hormones by administering anabolic sex hormones will be discussed under treatment.

It must be emphasized that, however promising these recent speculations may be, the essential cause of osteoporosis remains unknown.

CLINICAL PICTURE

Although there is no accurate information regarding the general incidence of this malady, there is some evidence to suggest that it occurs "physiologically" as a gradual accompaniment of old age. The back pain and "round shoulders" of old people may be due to a mild form of osteoporosis. The elderly gentleman whose femur fractures with minimal trauma and heals with maximal difficulty may be a victim of senile osteoporosis. The female patient in her forties or fifties, who complains of the gradual onset of back pain, or who feels a sudden snap and sharp back pain on lifting a heavy object may suffer from postmenopausal osteoporosis. Although these are the most common cases, osteoporosis may occur at any age. The various conditions with which it may be associated have already been enumerated.

The natural course of osteoporosis is to chronicity. Simple fractures may take months to unite and the slightest trauma may result in recurrent fracture at the healed site.

The spine is chiefly affected, although no bone may escape. Radiologically the bone is less dense than normal. There is a thinning of cortical bone and an enlargement of marrow spaces. The weakened bone, unable to support the body strains, crumbles and cracks. Vertebral bodies collapse and the spine may shorten or become kyphotic.

Osteoporosis may enter into the differential diagnosis of back pain, kyphosis or a pathological fracture. The diagnosis is established by X-ray evidence of generalized bone deficiency with normal calcium and phosphorus levels in blood and urine. When this state is observed, possible accompanying syndromes listed above must be excluded. Following this, there commonly remains a choice between the diagnosis of senile, postmenopausal and acute idiopathic osteoporosis. This choice is at present seldom significant since treatment is the same in each.

TREATMENT

There is at present no specific therapy for osteoporosis. The methods which

have been employed to date will now be briefly discussed.

High Calcium and Phosphorus Intake

The theory that senile and postmenopausal osteoporosis arise from long continued calcium and phosphorus deficiency seems to have originated with Muelengracht, a Danish investigator. This author reported a series of 19 patients suffering from what he termed "osteomalacia of the spinal column." To all intents and purposes these patients appear to have been suffering from what is termed generalized osteoporosis in this country. Muelengracht felt he discovered a reason for a prolonged deficiency of calcium and phosphorus intake in the history of each of these patients. On this basis, the author treated his cases rather haphazardly, with high calcium and phosphorus diets and Vitamin D. He noted symptomatic improvement with lessening of pain but was unable to demonstrate any increased calcification in bone by X-ray. He performed no balance studies on these patients.

Owen, Irving and Lyall investigated 7 male patients all about 70 years of age and all accustomed to a low calcium intake. By balance studies, these authors demonstrated that on a calcium intake of 200-300 mg. per day, these patients showed a slightly negative calcium balance or were actually in equilibrium with regard to this mineral. When their calcium intake was increased to 550 mg., however, calcium was strongly retained. These authors believe that some degree of osteoporosis occurs during a long period of calcium deprivation but that the mobilization of skeletal calcium tends to be gradually diminished until a state of minimal equilibrium is reached. All the cases in the present series reached a satisfactory level of calcium absorption when the intake was increased without added vitamin D.

Bauer and Marble, Boothby and Snell have reported isolated cases of osteoporosis in women 54 and 65 years old respectively. In each case the previous diet had been deficient in calcium and phosphorus. Balance studies were conducted and increased retention of these minerals was found when their intake was increased. When Vitamin D was given, a more positive balance for each mineral was obtained. Both patients showed improvement in symptoms but there is no mention of improvement in radiological appearance of the bones.

Kesson, Morris and McCutcheon fed a calcium enriched diet and Vitamin D to 8 osteoporotic patients and one patient with normal bones. In each case a marked increase in calcium retention occurred but the normal patient showed a lower retention than the osteoporotics. These patients had balance studies performed 14 and 18 weeks after treatment had been commenced and similar calcium retentions were found. Again no radiological evidence of increased calcification was demonstrated. These authors also investigated 5 female patients during 6 months of oestrogen therapy. No balance studies were performed and no change was seen in the X-ray. The authors concluded that oestrogen plays no part in the treatment of osteoporosis.

Black, Ghormley and Camp of the Mayo clinic report a series of 72 patients suffering from senile osteoporosis—probably the largest series reported in the literature to date. These authors propose, as objects of treatment, relief of pain, prevention of further de-

formity and restoration of normal bone. Their method of therapy involves the following points:

1) Recumbency in bed is advised since this tends to relieve pain and prevent progressive deformity. The authors warn that this procedure should not be carried to far since it may prove impossible to get the patient on his feet again.
2) Heat and massage to the back is used to relieve pain and muscle spasm.
3) Support for the back is suggested.
4) Dietary treatment consists of 40 Gm. tribasic calcium phosphate and 4 cc. cod liver oil three times daily.

On this regimen, 58% of 45 patients were improved or cured as far as symptoms were concerned. When no calcium, phosporus or Vitamin D was given but physical therapy and support to the back was prescribed, 33% of 15 patients were improved or cured.

HORMONAL TREATMENT

Albright and his fellow investigators have used gonadal hormone therapy in disuse atrophy of bone and in the following forms of osteoporosis:

Postmenopausal osteoporosis
Senile osteoporosis
Idiopathic osteoporosis
Osteoporosis of Cushing's syndrome
Congenital hypo-oestrinism

These authors performed extensive metabolic studies on a few patients in each of the above groups. Their results were good in all cases except in those of idiopathic osteoporosis. The effect of oestrogen and androgen together was greater then the effect of either alone. Progesterone alone or in combination with oestrogen had no definite effect on calcium metabolism.

The authors suggest that a high protein diet is probably indicated in these cases but since the disease is not one of calcium and phosphorus metabolism, high intake of these minerals and Vitamin D are probably not indicated. They advise against prolonged immobilization because of the danger of superimposed atrophy of disuse.

A number of side effects encountered in gonadal hormone therapy should be remembered. The harmful effects of oestrogens are:

1) Endomentrial hyperplasia

It is suggested that oestrogen therapy be interrupted periodically every 4 to 6 weeks for 7 to 10 days to allow for oestrogen-withdrawal flowing. As an alternative, progesterone may be administered for 5 days every 4-6 weeks to allow progesterone-withdrawal flowing.

2) Water and sodium retention

In elderly patients, especially those with low serum proteins, oedema may result from prolonged administration of steroids. This may be controlled by a low sodium diet and the administration of ammonium chloride.

3) Carcinogenesis

There is a possibility that continued administration of oestrogens may lead to cancer. Any vaginal bleeding occurring other than after an interruption of therapy should be fully investigated. Vaginal smears taken every six months provide a further safeguard.

The greatest objection to testosterone administration in females is its masculinizing effects. In most cases, these effects can be avoided by keeping dosages below 200 mg. per month. In males to whom testosterone is given, un-

due enlargement of the prostate may occur and should be watched for. Oestrogen may be given at the same time to neutralize this effect.

In general, Albright finds that the results of gonadal hormone therapy have been good. Pain is eliminated within weeks or months. There has been an increase in weight and general well-being. He has found it difficult to demonstrate increased bone density radiologically but states that recent films of several of the longest treated cases are convincing.

TREATMENT OF MISCELLANEOUS FORMS OF OSTEOPOROSIS

Mention has been made of several other forms of ostoeporosis, namely those forms occurring in malnutrition, Vitamin C deficiency, hyperthyroidism and acromegaly. In each of these diseases, treatment is aimed at the primary cause rather than at the osteoporosis itself.

THE PLACE OF ORTHOPAEDIC PROCEDURES IN THE TREATMENT OF OSTEOPOROSIS

It is a well-known fact that rarefaction occurs in bones of a limb immobilized because of fractures. This fact is well borne out by a case quoted by Albright, Burnett, Cope and Parson. The patient was an adolescent male who suffered a fracture through a solitary bone cyst. He was immobilized extensively and soon showed signs of hypercalcaemia with kidney failure. The picture was so suggestive of hyperparathyroidism that his neck was explored surgically. Normal parathyroid tissue was found. When he was mobilized, his symptoms improved remarkably and kidney function returned to normal.

It is obvious that immobilization of an osteoporotic skeleton is to be avoided where possible. When pain is excessive, however, some form of support for the osteoporoic spine may be necessary. The investigators in the Mayo clinic suggest high-backed corsets with steel stays or a Taylor brace. In any event, pain and disability tend to subside when appropriate treatment, either dietary or hormonal, is administered and it would seem wise to discontinue immobilization as soon as absence of pain makes this possible.

RESULTS OF TREATMENT

Thus when high calcium and phosphorus diets are administered a positive calcium balance results. When sex hormones are given, a positive calcium balance results. Often the patient feels better, pain is relieved or abolished within three months, and fractures may slowly heal. A positive calcium balance indicates that the patient is excreting less calcium than he ingests *i.e.* he is retaining calcium in his body. But X-rays do not show any material improvement in the density of the bone shadow. What does this mean? There are several possibilities. First, it is known that X-ray methods at present are not accurate enough to show anything but gross changes in bone density. Secondly, it is possible that the healing process may be an extremely slow one, so that gross improvement may not be evident for two, five or more years. In addition, there is the disturbing possibility that calcium may be deposited in the soft tissues rather than in bone, especially in older patients.

Experiments with radioactive tracers now in progress may help to explain the fate of the retained calcium. But whatever its fate, the essential poblem in osteoporosis will probably be answered by further study of the metabolism of the organic matrix. Now, for the first time, it may be possible to produce osteoporosis experimentally by the administration of the glucogenic hormones of the adrenal cortex.

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HYPERTENSIVE DISEASE IN PREGNANCY

AMALA RAMCHARAN, M.D.

HYPERTENSIVE DISEASE or essential hypertension, though not a true toxaemia of pregnancy, is usually classified under the toxaemias since it tends to simulate pre-eclampsia and renal disease and to precipitate the toxaemic state during pregnancy.

According to Stander hypertensive disease signifies an elevated blood pressure without any apparent associated pathology except insofar as the vescular system may be involved.

This disease may be classified into two distinct forms, which have been recognized since 1914 by Volhard and Fahr *viz:*

(1) Benign hypertension.

(2) Malignant hypertension.

Stander goes on further to divide the condition into four gradations:

(1) Benign hypertension, where the blood pressure is not raised to extreme degrees, with no albuminuria and usually no symptoms
ally no symptoms.

(2) More marked hypertension, retinitis.

(3) Mild vasospastic retinitis and sclerotic changes in the arterioles but without oedema of the discs.

(4) Malignant form with marked organic narrowing of the arterioles and with diffuse retinitis and edema of the discs.

DeLee and Greenhill state that 25 per cent of all cases of toxaemias have essential hypertension.

The disease is frequently associated with obesity and occurs more in tense overworked city dwellers than in the more phlegmatic leisurely rural population.

ETIOLOGY

Stander attributes the etiology as being due to morphological and chemical changes playing a role in the production of hypertensive disease.

According to Hussay, a probable etiological factory may be certain toxic substances acting on the walls of the blood vessels; that the substances have their origin in the placenta and perhaps pituitary.

Volhard describes similar substances as sensitizing the vessel walls to pressor bodies.

DeLee states that probably a hereditary tendency exists in hypertensive patients. Some patients, he says, have a marked constitutional abnormality which may lead to the development of hypertension.

PATHOLOGY

Benign and malignant nephrosclerosis are the pathological conditions corresponding to the clinical conditions benign and malignant hypertension. According to Boyd, in the benign form of the disease in which the onset is gradual and pursues a long-continued course for many years, the characteristic gross finding is a small, hard, granular kidney, which is shrunken and referred to as "the primary contracted kidney". The characteristic microscopic lesions are (a) hyaline degeneration and (b) elastic hyperplasia or elastosis. Hyaline degeneration, the commonest manifestation of arteriolosclerosis, is best seen in the smallest vessels. There is first of all a smooth acidophilic thickening of the subintimal tissue which goes on to

involve the entire thickness of the wall, causing narrowing of the lumen and may indeed lead to complete obliteration.

Elastic hyperplasia occurs moreso in the larger arterioles and medium-sized arteries. Here the internal elastic layer is spilt into several layers. A proliferation of endothelial cells may take place and become intermingled with the new elastic fibres. The elastosis may spread to the intima and to the media, thus converting a muscular type of artery into an elastic type.

Besides the vascular changes, there are later ischaemic changes in the glomeruli which the arteries supply, the glomerular tuft becoming converted into a hyaline mass later on, followed by fibrosis of the whole capsule. The corresponding tubules atrophy. Between wedge-shaped patches of atrophy are areas of normal or dilated tubules.

In the malignant form of hypertension, which has an abrupt onset and runs a very short course, lasting a few months rather than years, there may be no renal lesion for a long time. The patient may succumb to cerebral haemorrhage, cardiac failure or uremia and in such cases the renal damage is great. In younger patients, with severe hypertension running an acute course, the gross appearance of the kidney is characteristic, being of normal size or enlarged, with a smooth surface and no atrophy. If the process was prolonged, the organs are contracted and granular. Haemorrhages may appear on the surface, hence the name "flea-bitten kidney".

The characteristic microscopic lesions are (a) cellular hyperplasia and (b) arteriolar necrosis. The hyperplasia involves intima and media. In the necrotic process the whole thickness of the vessel wall becomes structureless. Besides the above vascular changes, the kidneys also show focal glomerulitis and tubular hyperplasia.

Pathological changes also take place in the heart and brain. There is cardiac hypertrophy and dilatation of the left ventricle followed by left auricular hypertrophy. Heart failure due to either hypertrophy or dilatation or to coronary sclerosis is the cause of death in 60 per cent of patients. Cerebral arteriosclerosis results in thrombosis or haemorrhage.

BLOOD PRESSURE IN NORMAL PREGNANCY

Irving states that in all normal pregnancies there is a slight elevation of pressure. The age, nationality and parity all have an influence on blood pressure. The normal range of blood pressure in pregnancy is 100-130 systolic.

According to Donaldson, however, no increase in blood pressure occurs in pregnancy, nor is there any fall soon after labour.

PHYSIOLOGICAL ASPECTS OF HYPERTENSION

Blood pressure, we know, is maintained by cardiac output, tonus of the vascular bed, volume and viscosity of the blood and peripheral resistance. In essential hypertension all of these factors except the last are apparently normal while it is believeed that peripheral resistance is increased due to involvement of the arterioles. This increased resistance may be the result of morphological changes in the walls of the arterioles or by vasoconstriction of nervous or chemical origin.

In the early stage of the disease the increased resistance is probably due to functional contraction of the arterioles, whereas later, the probable cause is morphological changes in the walls of the arterioles. In hypertensives the arteriolar responses to certain agents, such as body warming and chilling, epinephrine, pituitrin and local heat or cold are essentially normal. Also experiments on the abolishment of vasoconstrictor tone and blocking of sympathetic vasoconstrictor impulses show that the sympathetic tone is normal.

From these findings we may conclude that hypertensive disease is probably due to unknown humoural or chemical stimulation causing vasoconstriction throughout the entire vascular system.

Goldblatt in 1932 produced hypertension in animals by constriction of renal arteries. Such hypertension may result from renal ischaemia and may be dependent upon hormonal factors arising from the adrenal cortex or kidney.

Many workers in this field have proved that reduced renal blood flow produces hypertension through a substance "renin" formed in the ischaemic kidney. Renin acts on a blood globulin (hypertension precursor) to produce a pressor substance (angiotonin or hypertensin) which causes vasoconstriction. This pressor substance may be destroyed by another enzyme (angiotonase) which is supposed to be present in both blood and body tissues.

SIGNS AND SYMPTOMS OF HYPERTENSIVE DISEASE

In the mild form of hypertension the blood pressure is not extremely high. The elevated pressure which occurs is not associated with signs or symptoms of kidney involvement. There is no albuminuria, only slight changes in the retinal blood vessels take place and the patient states that she feels well.

Some of the early symptoms are:

(1) Headache.
(2) Vertigo.
(3) Restlessness.
(4) Insomnia.

Later on there may be symptoms of left heart failure and hypertensive encephalopathy such as intense headache, vomiting, drowsiness and coma. Nocturia is common.

The signs found in more severe cases are:

(1) A hard pulse difficult to compress.
(2) Tortuosity and thickening of peripheral vessels.
(3) Varying degrees of tortuosity of retinal arteries.

There may be narrowing of the arteries, nicking of the veins and in advanced cases:

(1) Papilloedema.
(2) Haemorrhage.
(3) Exudates.

But these are more often found in the malignant stage. The blood pressure in the benign form is over 140 mm. Hg systolic and over 90 mm. Hg diastolic.

In the malignant form of the disease the retinal arteries are sclerosed; the walls are thickened and irregular; there is indentation of the veins at the arterio-venous crossings; engorgement of the retinal veins and the appearance of flame-shaped and rounded retinal haemorrhages. There may be oedema of the retina, cotton wool patches and a macular star. This is, in brief, the picture of "albuminuric retinitis."

THE INTER-ACTION OF PREGNANCY AND HYPERTENSIVE DISEASE

According to most of the older texts, pregnancy in all cases of hypertensive disease should be avoided; and if pregnancy occurs, it should be terminated in the more severe forms of the disease. Today, the approach to the problem is somewhat different, due to recent investigations made in hypertensive patients.

If a patient has an elevated blood pressure without demonstrable disease before she became pregnant, it is probable she is suffering from hypertension. But if her blood pressure is normal until mid-pregnancy and then begins to rise, it is due to a toxaemia directly associated with pregnancy and is not essential hypertension.

Hypertension may appear before pregnancy begins or may appear for the first time during gestation. It is possible that pregnancy may be playing a role in the etiology of essential hypertension, because the pregnant state is occasioned by vascular changes, particularly spasms of the arterioles.

Chesley, who has done much work in the study of pregnancy and hypertension, has said that although the effect of hypertensive disease upon pregnancy is known, yet the effect of pregnancy upon hypertensive disease is little known. He goes on to say that pregnancy is immediately hazardous to the hypertensive woman and foetus, and once through the pregnancy the woman has suffered irreparable damage which shortens her life expectancy, though this is not supported by much evidence.

RENAL FUNCTION IN RELATION TO PREGNANCY WITH ESSENTIAL HYPERTENSION

In considering this relationship two points must be taken into account, namely:

(1) The significance of the apparent increase in renal blood flow which develops when the patient with essential hypertension becomes pregnant.

(2) Clinical implications of the renal function tests made before, during and after pregnancy complicated by pre-existing vascular disease.

The increase in renal blood flow during pregnancy appears to be real, but is slight. The blood flow falls after delivery—blood flow in essential hypertension parallels the blood flow in patients with specific toxaemia, *i.e.*, blood flow is normal or slightly elevated during pregnancy but in those who develop a persistent hypertension, renal ischaemia appears immediately post-partum. Most essential hypertensive patients show a striking decrease in blood pressure at mid-pregnancy. Some workers have reported a temporary rise in blood pressure for weeks after a normal pregnancy.

The theory regarding increased renal blood flow in pregnant hypertensive patients postulates the placenta as being the cause, *e.g.*,

(1) The sudden contraction of the total vascular bed through the elimination of the large circulation of the maternal portions of the placenta might affect the blood pressure for a short time.

(2) Hormones of placental origin have a direct effect on renal blood vessels, but no evidence has been produced as yet to prove this.

It is known that estrogens and other sex steroid hormones have some effect on peripheral circulation. It is thus possible that the blood flow of the kidney in hypertensive patients is maintained by some such substance from the placenta whose loss at delivery is at once followed by relative renal ischaemia.

There has also been failure in finding signs of deterioration of renal function after pregnancy in women with essential hypertension.

In conclusion we may note that:

(1) Renal function studies on patients with essential hypertension indicate that pregnacy is associated with a slight temporary increase in renal blood flow.

(2) Pregnancy itself when uncomplicated by specific toxaemia does not cause any deterioration of renal function in a woman with essential hypertension.

DIFFERENTIAL DIAGNOSIS

Essential hypertension complicating pregnancy is often confused with pre-eclampsia, because of elevated blood pressure, commonly associated with pre-eclampsia.

In essential hypertension the history is of importance—*e.g.*, a history may be given of the condition being present before the onset of pregnancy. Thus hypertension is detected early in gestation.

Pre-eclampsia may be ruled out unless there is the possibility of superimposition of pre-eclampsia on the underlying vascular condition. Confusion exists when essential hypertension appears for the first time late in gestation. In these cases the symptoms and signs occurring are:

(1) High blood pressure.
(2) Pitting oedema.
(3) Albuminuria: trace to one plus.
(4) Enlargement of the heart and retinal vessel changes in prolonged cases.

Where a sudden rise in blood pressure occurs above 140 mm. Hg in a woman with a blood pressure previously below 140, the possibility of pre-eclampsia must be considered.

DIAGNOSIS OF ESSENTIAL HYPERTENSION

The diagnosis depends on:

(1) A knowledge of the patient's past history.
(2) The extent and course of the hypertension.
(3) An examination of the eye-grounds.
(4) An evaluation of kidney function.
(5) A careful clinical consideration of the signs and symptoms.

TREATMENT

The treatment of this disease is purely empirical as the etiology is unknown.

Mild Cases

(1) The activity of the patient should be restricted.
(2) There should be sufficient sleep.
(3) Care of the bowels should be stressed.
(4) It should be seen that the patient urinates a sufficient amount.
(5) Table salt should be omitted.
(6) There should not be too much use of alkalis.

Slightly advanced cases should have daily bed rest and mild sedative, such as half a grain phenobarbital t.i.d. should be administered.

MALIGNANT HYPERTENSION

(1) The patient should remain in bed.
(2) Phenobarbital grains I t.i.d. should be administered.
(3) No table salt is allowed.
(4) Fats are restricted.
(5) No form of sodium is given.
(6) A daily bowel movement is achieved with or without the use of a cathartic.

If the urine output is less than 1000 cc. daily, then 500-1000 cc. of a 20% glucose solution are injected intravenously three times daily. This is injected slowly over 30 to 60 minutes for each injection in order to produce a diuresis.

If the blood pressure still rises in spite of the above treatment, and if the eye-grounds show alterations in the vessels, then the pregnancy should be terminated.

Caeserian section is seldom necessary. The method for emptying the uterus depends on the following conditions:

(1) The severity of the hypertension.
(2) The size and condition of the baby.
(3) The presence of disproportion or other causes of dystocia.

It should be remembered that pituitary extract must be avoided in a woman with hypertension.

More recent observations made on patients with essential hypertension will serve to either clarify certain points or further confuse pre-existing ideas on the subject.

Grollman states that the fact that hypertension follows manipulation of the kidney, as well as the high incidence of hypertension observed in the human being with kidney disease, leaves little doubt that the experimental disease as well as many cases of clinical hypertension is secondary to dysfunction of the kidney.

Smithwick, working on lumbodorsal sympathectomy, shows the relation of essential hypertension to pre-eclamptic toxaemia. There is a marked lowering of hypertension following the operation which allows patients to proceed uneventfully through pregnancy. The patients with hypertension previous to operation would be serious risks for pregnancy. One patient in particular who with a previous pregnancy developed severe cerebral and visual disturbances had to have the pregnancy terminated at seven months. After sympathectomy she went uneventfully through a normal full-term pregnancy. In spite of this operation, however, some of the patients develop pre-eclamptic toxaemia.

CONCLUSIONS

From the above discussion it may be seen that no one knows the whole story of hypertensive disease, whether occurring in the pregnant or non-pregnant patient. There is indeed need for much more research into the problem and until more light is thrown on the etiological aspects of the condition, one cannot hope for too much in the way of successful treatment of the disease.

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WELL WATER METHAEMOGLOBINAEMIA IN INFANTS]

A. C. IRWIN, B.A., 5T1

INTERMITTENT OR PERSISTENT cyanosis in a young infant may be due to methaemoglobinaemia rather than to such serious conditions as congenital heart disease, abnormalities of the respiratory tract, diaphragmatic hernia and enlarged thymus.

CAUSES OF METHAEMOGLOBINAEMIA

1. Drugs and chemicals. These are the most frequent causes of this condition and include such substances as acetanilide, phenacetin, aniline, nitrobenzene, potassium chlorate, one of the nitrates and more recently one of the sulphonamides. Several cases have been reported (1), (2), in which bismuth subnitrate used in the treatment of diarrhoea, led to methaemoglobinaemia.

2. Congenital. This is a rare cause (3). Occasionally, this form may be familial (4).

3. Contaminated well water. This should be considered as a possible cause of cyanosis in an artificially fed infant. It is with this form that I have made a review of some of the more recent literature.

LOCATION OF SOME REPORTED CASES

In North America, cases have been reported from a rather wide area. In 1940, Schwartz and Rector (5) described a case in Montana and this was followed in 1945 by 2 cases in Iowa (6). In 1946, Faucett and Miller (7) described a case in Kansas.

In 1947, Medovy *et al* (8) described two cases in Canada—one in Dryden, Ontario and one south of Winnipeg. This was soon followed by Goluboff (9) describing a case near Saskatoon. More recent Canadian cases include those of McLetchie and Robertson (10) near Regina and those of Medovy (11) near Winnipeg.

MECHANISM OF METHAEMOGLOBIN FORMATION

When ingested, nitrates are reduced to nitrites and finally to ammonia, in which form they are excreted. Nitrate reducing bacteria flourish when the pH is higher than 4 and an infant's gastric juice is usually above this until after 2 months of age. In high concentrations, some of these nitrites may be absorbed by the bloodstream before being reduced further. Cornblath and Hartmann (12) have reported the experimental production of methaemoglobinaemia in infants by the introduction of nitrates into well water used in their formulae.

A molecule of the nitrite ion reacts with two molecules of haemoglobin to form methaemoglobin which, although not toxic in itself, is unable to carry oxygen. Normally, it is present in the blood to the extent of 1 per cent and is reduced by an enzyme system within the red cells. In great excess, this mechanism may break down and the amount of methaemoglobin rise to dangerous levels.

SIGNS AND SYMPTOMS

These include the following:

(1) Cyanosis, often varying from day to day.
(2) Increased respiratory rate.
(3) Listlessness.

DIAGNOSIS

This is made clinically by the presence of a greyish-brown cyanosis and a chocolate color of the blood. Chemical analysis of the blood will demonstrate nitrites and the methaemoglobin can be identified by its characteristic absorption spectrum in a spectroscope.

PROGNOSIS

If the condition is recognized promptly, and the source of water changed, spontaneous recovery usually occurs in 36 to 48 hours. The Minnesota State Department of Health recorded 14 deaths in 139 cases over a period of 2½ years (13).

PROPHYLAXIS

The ideal feeding for a young infant is breast milk. Where this is impossible and where the water supply is suspected, the safest artificial feedings are those that require the least water in their preparation. In the decreasing order of safety these would be:

(1) Undiluted acidified milk mixtures.
(2) Cow's milk mixtures.
(3) Evaporated milk mixtures.
(4) Dried milk.

It has been suggested that lactic acid can be added to the mixture to a concentration of 0.5 - 1.0 per cent. This will decrease the nitrate reducing bacteria of the gastrointestinal tract.

TREATMENT

In severe cases, one must give methylene blue I.V., the dosage being 1.0-2.0 mg/Kg. In an 8-lb. infant, ½ cc. of a 1 per cent solution would be a suitable dose. Since methylene blue is an oxidizing agent, its use in this situation would seem illogical but clinical experience has demonstrated its value.

Bodansky (14) (15), has offered an explanation. The reduction of methaemoglobin to haemoglobin is brought about by the reduced form of the coenzyme diphosphopyridine nucleotide and this action is greatly accelerated by methylene blue. The reduced form of this enzyme becomes oxidized whereas methylene blue is reduced to leucomethylene blue. The latter then reduces the methaemoglobin to haemoglobin. This is a cyclic reaction and will continue as long as the reduced enzyme is available.

SURVEYS OF WELLS

In Saskatchewan, a survey of wells begun in 1948 showed that 25.5% contained over 20 parts per million and 16.1% contained over 50 p.p.m. of nitrates. 95% of those with a high nitrate content were dug or shallow wells. Nitrates in excess of 20 p.p.m. are regarded as potentially dangerous to infants. In some of the fatal cases, the well water contained over 1000 p.p.m.

The majority of the wells in the Saskatchewan report (16) were also contaminated whereas in an Illinois survey, no correlation existed between the high nitrate content and bacterial contamination. A survey of wells in the Edmonton area showed that a marked fluctuation in the nitrate content of a single well can occur throughout the year. (17)

The principal source of nitrates in

well water is the bacterial decomposition of animal or human excreta that has found its way into the wells. Although this is the consensus of most investigators, Medovy believes that the problem is due to a high nitrate concentration in the soil.

CONCLUSIONS

Physicians should be aware that such a condition exists and have sterile methylene blue available for emergencies. When water from any well is to be used in the preparation of infants formulae, it should first be tested in the Provincial Laboratory for its nitrate and nitrite content. However, this problem would be non-existent if breast feeding were continued for the recommended length of ime.

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EDITORIALS

"ALL THE WORLD'S A STAGE"

The tragedy of sickness is a universal drama which the medical profession constantly strives to turn into comedy by supplying new direction and fresh dialogue to the troubled players. In each act, the roles played by the doctor and his associates must be rehearsed well. The script must be complete and the props adequate.

We have the opportunity to perform on our local stage and effect a wizardry of changing tragedy into comedy. This opportunity includes a choice of scripts, a choice of stages and a choice of props; each one is adequate, complete and in quantity. With all these, we rarely consider that we are particularly fortunate actors. Rarely do we consider that there are similar tragedies being enacted on other portions of the stage where wizardry is lacking.

In these areas, there is no lack of enthusiasm on the part of the apprentices; they are eager to play a competent role in the drama presented to them. What is lacking consists of textbooks and equipment with which to learn, supplies and facilities with which to perform.

The spotlight is on these actors with the establishment of All-varsity Aid to selected colleges in Pakistan and India. The undergraduates of Medicine are being approached to give assistance in the most appropriate way to those who have assumed similar roles to theirs in a situation where need is greater and opportunity less. We are asked to step out of our self-made limelight and offer things which we take for granted to a

grateful people who will accept our offerings as luxuries.

In assessing our approach to improving the setting of this specific drama, no one will complain if each actor sacrifices his lines in order that a less favoured player may succeed. All-varsity Aid looks to us to help our colleagues in other lands by functioning as a sincere supporting cast.

ALTRUISTIC ALUMNI

Following graduation we will have an opportunity to become members of the University of Toronto Medical Alumni Association. It is hoped that we will avail ourselves of this opportunity.

It is not the purpose of this editorial to outline completely the activities of the Association. There are, however, certain tangible expressions of interest in us as undergraduates, concerning which some members of our body may not be aware.

Some years ago, the Association established a fund to provide bursaries and scholarships to undergraduates in the Faculty. Increasing alumni has enabled the Association to expand this scheme and this year four Bursaries of $100 are available to students from any year who are in need of financial assistance, as are six Scholarships of $200, one for each of the six undergraduate years.

The Association has also a special Graduate Bursary Fund in Psychiatry to assist recent graduates who, in the opinion of the Professor of Psychiatry, and the Faculty of Medicine, are to be encouraged to further their training in this specialty.

Loans, from a recently broadened Medical Alumni Association Loan Fund are now also available to undergraduate, as well as graduate, students.

Alumni interest is not solely confined to financial matters. Feeling that University of Toronto medical students would be interested in, and benefited by, a forum discussion on medical practice from the point of view of the experienced practitioner, the Association has, for some years, sponsored a Panel Discusison on Practice for members of the graduating year. This Panel has been most enthusiastically received, and is a source of much valuable information.

Just prior to Convocation, a Graduation Dinner is held by the Association to which are invited members of the graduating year and veteran medical graduates of the Convocation fifty years previous. This dinner is a significant event, and provides the graduating doctor with a point of contact with his Alumni Association.

Those activities of our Medical Alumni Association which are of special interest to us as undergraduates have been outlined. The sphere of activity of the Association is not, of course, limited to these interests alone. It is hoped that, as graduates, we will become members of the Association. It is an active one, deserving of support.

R. L. S.

A PROBLEM IN DIAGNOSIS

A. KLISOWSKY, 5T1

A. C., A TWENTY-FOUR YEAR OLD white female was admitted to the surgical service of Toronto General Hospital on October 8, 1950. She complained of aching pain in her right arm of eight months duration.

Ten years ago the patient received a shell wound in her left femur during World War II in Poland. The wound took six months to heal and has remained healed, with no disability since. In February, 1950, while employed at the Queen Elizabeth Hospital she suffered from a prickly sensation in digits 3, 4 and 5 of her right hand. This was followed by infection in these fingers which cleared up spontaneously in about three days. This was followed in a few days by a small nodule the size of a bean over her right arm below the deltoid insertion. This nodule was tender and painful. The patient applied heat to it and obtained relief from pain after about three weeks.

In June she noticed an occasional ache in her right arm coming on at night. Eight weeks prior to admission the ache became more severe and occurred during the day as well and the nodule increased in size. The arm was now painful on movement.

The patient has had a feeling of malaise, increasing fatigue and loss of appetite with no true chill or night sweats in the last eight months. She states that she has lost some weight.

She gives a history of contact with tuberculosis with which her mother was afflicted.

Examination of admission revealed a well developed, pale, well nourished woman in no apparent distress; temperature 103 degrees F., pulse 95, blood pressure 105/70, W.B.C. 11,600, Hb 83 per cent. The other relevant findings were limited to her right arm. There was a small, tender, irregular, indurated nodule, 2 x 1 cm., in the right arm below the deltoid insertion. It was red and warmer than the surrounding tissues.

Her chest X-ray on admission showed healed tuberculous lesions. The X-ray report of the right arm was "an osteoplastic lesion with irregular narrowing of the medulla at the centre of the right humeral shaft. There is marked thickening and sclerosis of the cortex with a thin lamina of sub-periosteal new bone on each side. The site is against osteomyelitis but other features favour it."

DIFFERENTIAL DIAGNOSIS

Considering the history, nature and site of the lesion, the following were included in the differential diagnosis:

1. Osteomyelitis.
2. Tuberculosis.
3. Ewing's sarcoma.
4. Syphilis.

A lesion such as this, associated with fever and leucocytosis preceded by a history of infection on two occasions, was quite in keeping with a diagnosis of *osteomyelitis*. The source of the present infection was, however, difficult to determine. Whether her femoral injury ten years ago was followed by osteomyelitis was not proven. If it were, then it is conceivable that the organisms were harboured at the site and were the source for a vascular dissemination at the onset of the present illness. It could also be a sequel to her digital infection

of last February. This diagnosis was questioned when the patient failed to respond to antibiotic therapy as dis-discussed below.

Her history of contact with *tuberculosis* and the X-ray evidence of healed tuberculous lesions in her chest made this disease a possibility in the diagnosis. Tuberculosis of a long bone usually involves an extremity but as with most medical phenomena there is always an exception and a tuberculous lesion can occur in the shaft. It should be noted that during her course of treatment a tuberculin test was performed and a strongly positive result was obtained. This added to the difficulty of ruling out a disease process which did not present a true clinical picture. However, this evidence was not considered in the immediate treatment of the case.

Ewing's sarcoma often presents the clinical and laboratory findings of osteomyelitis and is often very hard to differentiate from this disease. Even after incision the material obtained can easily be mistaken, in the gross, for pus. The site of the lesion is a common one for Ewing's. The X-ray picture was not typical of Ewing's which is essentially an osteolytic process. It will not respond to antbiotic therapy but does readily subside when radiated.

Syphilis could produce a localized lesion in the shaft of the humerus. This is essentially a periostitis and the X-ray picture was not suggestive of this process. A gumma is painless so the clinical picture rules it out. There was no evidence of the disease elsewhere and a negative Wassermann was reported.

PROVISIONAL DIAGNOSIS

Osteomyelitis of the right humeral shaft.

TREATMENT AND CLINICAL COURSE

The patient received 400,000 units penicillin while investigation proceeded. On October 10 her W.B.C. was 14,000 with 81 per cent neutrophils; Westergren sedimentation rate 90 mm/hour; acid phosphatase 2.5 units and alkaline phosphatase 5.7 units (King-Armstrong); blood culture negative.

She remained febrile (about 100 degrees F.) and the nodule on her arm increased in size. After three days a large soft tissue mass could be palpated outside the shaft of the humerus; it was considered to be fluctuant, and that there was a considerable amount of pus present thereby diminishing the effectiveness of antibiotics. She was given sulpha drug (Trulfa) 1 Gm. q4h with an equal quantity of sodium bicarbonate, with no resulting drop in temperature. The mass was incised and about 10 cc. of pus escaped. A cloaca was found on the antero-lateral aspect of the upper end of the humerus. The cloaca was enlarged and the wound packed open with acriflavine and glycerine gauze.

Direct examination of a swab from the abscess showed an occasional leucocyte but no bacteria. Culture of swab revealed *Staphylococcus albus.*

Four days after drainage of the abscess the patient was afebrile and feeling well.

FINAL DIAGNOSIS

Osteomyelitis of the right humerus.

ACKNOWLEDGEMENT

It is a pleasure to acknowledge the assistance of Dr. J. R. F. Mills during the preparation of this report.

HUMANISM AND MEDICINE

H. B. VAN WYCK

PART XIV

WILLIAM HARVEY AND THE CENTURY OF GENIUS

After the centuries of the Renaissance (the 14th and 15th), the new impulse to scientific inquiry and the enlarging horizons of both space and time began to stimulate advances in the physical studies, mathematics, and philosophy. The heritage of Greek science and classical literature, rediscovered by the "humanistic" revival of Europe, was the fruitful seed; and, in the 17th century, its harvest was the most abundant on record.

By the 16th century had appeared those great early text books to which Europe was ready to go to school—Leonardo da Vinci's (1452-1519) "Anatomical Studies", Leonard Fuch's (1501-1566) "Botany", and the astronomical works of Copernicus (1473-1543) and Tycho Brahe (1546-1601). In 1543 appeared a foundation-stone of modern biology, "On the Fabric of the Human Body"—the first systematic book on Anatomy, by Vesalius of Padua. At the end of the century could be heard the voice of the herald of the coming age—Sir Francis Bacon. While Europe was suffering from the growing pains of religious evolution, Bacon summoned men to new tasks with the enthusiasm and the sense of power inspired by the new discoveries. He bade modern man develop the critical spirit, discard the fallacious and blind worship of authority, and turn to the world of nature to discover peace and prosperity for mankind. In a notable sentence, typical of Bacon in its completeness, he described the symptoms of specious and unscientific work: "I do not endeavour by triumphs of confutation, or pleadings of antiquity, or assumption of authority, or even by the veil of obscurity to invest these inventions of mine with any majesty". In the preface to the "Novum Organum" he wrote: "I have not sought, nor do I seek either to force or ensnare man's judgments, but I lead them to things themselves, and the concordances of things, that they may see for themselves what they have, what they can dispute, what they can add and contribute to the common stock."

Here was a new note of optimistic faith in a programme for the understanding of things, and "hard, stubborn facts". It could be called a programme for the medical student: "to see for themselves what they are, what they can dispute, and what they can add and contribute to the common stock". William Harvey and his brilliant contemporaries must have been stimulated by these clarion phrases. For these builders of the new world of science were soon to appear; and, in a dynamic community of effort, they would produce that amazing crescendo of intellectual progress that nominates the 17th century as the century of genius.

Again was set flaming in the world that passionate curiosity which was first seen to glow in ancient Hellas; and again the necessity of a common co-ordinated effort was recognized anew if science was to go on fruitfully. Just as the ancient philosophers formed communities and schools of joint effort in Ionia, Elis, and Athens, so there now appeared in Europe a class of workers in varied fields of scientific investigation, each pursuing his ends in the closest spirit of co-operation. The Royal Society of England, founded in 1660, recalls in ideals and purpose that earlier brotherhood founded by Pythagoras. Scientific societies were founded throughout Europe; correspondence was copious between workers in each field; controversies as to priority attested the earnest zeal of these pioneers; and newly published work was eagerly and critically scanned. Science was ready to become international and was hailed by the young moderns as the survival of the religious international federation of the Middle Ages only in a new guise—that of a secular union of research into the secrets of nature. Such a non-national concentration of effort would be certain to bring Utopia and universal bliss. That in three centuries the physical sciences could produce a situation in which the products of science are so destructive that these threaten to shatter human brotherhood entirely was farthest from the thoughts of that great sponsor of science—Francis Bacon. The primal tragedy of history will perhaps prove to have been played at the point when science in the development of destructive methods withdrew from an unreservedly international programme. This may be necessity—but a necessity imposed by infernal fate.

But by the year 1600, it was obvious that modern physical science was no longer to be retarded by the casual attention of diffuse dilettantism or obscured by reliance on traditional beliefs or authorities. The profession of scientific investigation had taken a fresh root in the western world after a long, silent period of 1400 years. This time, its devotees were numerous and powerful enough to provide sturdy roots that might outlast the changing seasons of political upheavals. Never again, thought such optimists as Bacon, should defeatist philosophies and unlettered barbarians disturb the single purpose and steady progress of science. Bacon and his coterie could not foresee a civilization which would lose the stability of faith in religious and humanistic values; and, which thus foundered in materialism, would become a victim of its own technical devices. This descent to disaster has not been visible until our day. In the early 17th century, the new outlook in all fields promised, and did fulfil that promise, to do much for the material improvement of life.

The biological sciences began an attempt to express biological phenomena in physical terms. As noted above, these sciences tend to follow rather than lead the gains made in other physical fields. Thus, it is not surprising that Harvey did not appear until the work of Galileo had revolutionized the science of mechanics. Galileo, who visualized a completely mechanical universe, bade his successors investigate the body as a machine. Though this implied a determinism that had in its impersonal grip alike the celestial bodies, the insect, and man, the implication that humans like the stars "blindly run" (i.e., have no freedom) was not evident to the opponents

of Galileo or his fate would have been worse. Determinism is a good working hypothesis for the investigation of a biological field, provided that the biologist does not forget that the whole is greater than the sum of the parts and that biological data must be interpreted not only in isolation but also in terms of organism. It would appear that there is no basis in mathematically conceived physical and chemical truth for a vitalist concept as the explanation of the co-ordinated life of an organism.

The discovery of the circulation of the blood has permitted the investigation, on a vaster plain, of the activities of living organisms and may be said to form the matrix of the science of physiology. At the one epochal moment of Harvey's discovery, physiology became modern and now could strike new paths with confidence. The advancing sciences of physics and chemistry were giving physiology constantly improved techniques. From henceforth, the paths that had led in the past to blind ends could be avoided, or at least retraced, at early stages.

Thus among all the fascinating figures of this century, the student of medicine finds perhaps his chief interest in William Harvey (1578-1657). The circulation of the blood had engaged the curiosity of human minds from the earliest times. Even the pre-Hippocratic Greeks and Egyptians wrote about the pulse in disease; the relation of the movements of the heart and the peripheral pulse was discovered by Aristotle's time. Aristotle's observations were made on animals killed by strangulation; in these, the right auricle was so greatly dilated that he thought it part of the venous system and, hence, believed there were only three chambers in the heart. Aristotle concluded that the movements of the heart were due to a force upon which life depended; that the vessels about the heart were concerned somehow with the diffusion of this vital essence; while the vessels connected with the liver carried a nourishing factor. Both Erasistratus and Herophilus distinguished between arteries and veins. Erasistratus believed that in health the arteries were filled with the air essence or "pneuma", and that it was only when the "pneuma" was let out of the arteries as a result of injury or disease that they contained blood. He presumed that blood got into the arteries as a reflux from the veins. The fundamental meaning of the Greek "pneuma" is "air in motion"; the word then acquired such meanings as "breath of living beings", "emanation", "breath of life". The Latin equivalent is "spiritus" and thus the English word "spirits" came to express the various meanings of the Greek "pneuma". One might suggest that the "pneuma" or air was inferred because, if a body is examined some hours after death, the arteries seem comparatively empty and the blood may appear frothy due to glycolytic fermentation. This may occur by the action of bacterial agents—the anaerobic or coliform group. Galen's school, admitting the existence of a pulmonary circulation, held to the belief that the blood got from the right to the left side of the heart by passing through invisible apertures in the inter-ventricular septum. No progress was then made for 1,000 years. That there was a measurable and constant blood volume moving in a circle, and functioning ever in measurable physical and chemical terms was never dreamed of. The conventional Galenical view of the circulation

of the blood was that when food was absorbed from the alimentary canal, it was carried by the vena porta to the liver where it was converted into blood and endowed with "natural spirits". It then passed by way of the inferior vena cava to the right heart. Some blood now passed to the lungs, but most passed through the invisible pores in the interventricular septum into the left ventricle. Also as the heart dilated, air or "pneuma" was drawn from the lungs into the left ventricle. Thus, the ventricle contained crude blood, the air or "pneuma" and the innate heat of the heart; these combined to form blood endowed with "vital spirits"—to serve higher functions of vital organs. Are these "vital spirits" a premonition of oxyhaemoglobin? The blood on reaching the brain became endowed with "animal spirits" which is the highest form of biological energy. This phrase, "animal spirits", once a technical term in physiology, has survived in colloquial English, but its origin suggests that it is rarely correctly used. In the phrase, the adjective "animal" does not refer to the creatures lower than man in the scale of being. The word "animal" is here used in its original sense of "pertaining to the soul" for which the Greek word is "psyche" and the Latin equivalent is "anima". "Psychical spirits" would best translate the Greek "pneuma psych on", or the Latin equivalent "spiritus animales". Just as the "vital spirits" might be regarded as a vague foreshadowing of oxygenated blood, so the "animal spirits" of Galen, generated by the brain, forecast the nerve impulses of today. Such explanations of the terms used by Galen are essential for the understanding of the accepted medical doctrines of Harvey's time.

One might now summarize the errors of these doctrines which went far to hinder Harvey's discovery: For a millenium Galen and the world believed:

(1) That the origin of the veins was in the liver.
(2) That diastole was the most important movement of the heart.
(3) That the interventricular septum was permeable by invisible perforations.
(4) That the arteries contained air.
(5) That the motion of blood in both arteries and veins was a tidal ebb and flow.

Even Vesalius in the 16th century, though unable to find the interventricular openings, concluded that they must exist; or was he placating his enemies when he wrote: "We are driven to wonder at the handiwork of the Almighty, by means of which the blood sweats from the right ventricle through passages which escape the human vission"? The puzzle was not to be left long unsolved by the keen observers of the new Europe. Servetus, whom Calvin burned in 1553, had made a shrewd guess as to the value of the pulmonary circulation, and emphasized the role of the pulmonary valve. Sylvius, the teacher of Vesalius and Fabricius, Harvey's own teacher, had found valves in the veins. And such was the status of the problem when Harvey set to work. It has been noted that Shakespeare makes Brutus say to his wife, Portia:

"You are
As dear to me as are the ruddy drops
That visit my sad heart".

But, while this suggests motion, it means entrance, not expulsion and conveys at best only the conventional vague opinion abroad. Even the ancients recognized that the blood moved, but this is not the

circulation of the blood. What Harvey stated was that the blood moved in a circle and moreover proved that this was so.

William Harvey was born in 1578 at Folkestone, which faces across the English Cannel to Boulogne. One may imagine the boy Harvey playing in the sands in sight of the French coast and wistfully wondering about the new science that was filtering up from the universities of Italy and the mysterious Europe just beyond his horizon. There is the well-known picture of Drake at Plymouth playing bowls as he scanned the channel for the approach of the Spanish danger. A painter might well picture Harvey as a youth on the Kentish Coast gazing towards the horizon and seeing the vision of a beckoning Truth. He was the son of a prosperous farmer. Educated first at Canterbury, and graduated at Cambridge a Bachelor of Arts, he went to study medicine at Padua under Fabricius. He was now 19 years of age. He become a doctor of medicine, aged 24, in 1602, and returned to London to practise. His practice was lucrative. He was not one of those who lived in poverty to benefit humanity and perhaps deserves all the more credit for surviving the distractions of prosperity. He found time to give the Lumleian lectures to which he was appointed in 1615—a course that required a six-year period to discuss the material. The first lecture was in April, 1616—a month also notable for the death of Shakespeare.

Harvey began at this time formal research into the mechanism of the circulation. The results of his work he published in a monograph in 1628. "Exercitatio anatomica de motu cordis et sanguinis in animalibus". The book was published in Frankfort in 1628 by an unknown printer and was a miserable specimen of book-making with execrable paper printing. Few copies exist to-day. The first English edition did not appear until 1653. Harvey was an avid dissector and began his monograph by pointing out that the only method adequate for study of the circulation was by dissection and observation of the living animal body. He made minute descriptions of the action of the heart and vessels in many animal species. Noting that the contraction of the left ventricle caused a pulsation of the arteries, he dissected out an artery and put a ligature around it. Then, he made a nick in it on the side proximal to the heart. With each heart beat, blood poured out, but rapidly decreased in quantity until the heart ceased action. He repeated the experiment; but this time opened a large artery on the side of the ligature distal from the heart. No blood spurted out, and in a few seconds the heart dilated with accumulating fluid.

His next observations were made on the veins of the human arm after constriction by a band. By milking the veins, he demonstrated the one-way action of the valves. What seems clear to us had now been revealed for the first time. The arteries carried blood from the heart and veins carried it towards the heart. How did the blood get from the right heart to the left heart? Harvey pointed to the absence of the apertures postulated by Galen and Vesalius in the interventricular septum, and just as Servetus had done (although this was unknown to the Englishman), Harvey inferred the function of the pulmonary circulation. This sounds too obvious to us to require

statement. When Harvey first put this in print it sounded like a radical and dangerous heresy. For less than this, Vesalius had suffered coarse abuse and turning his back on his own genius, had gone into exile to Spain, the perpetuated influence of Galen thus claiming another victim. For the same iconoclasm, Servetus had been burned at the stake; and for no greater innovation, had Paracelsus been mobbed in Basel and eventually murdered.

Harvey next removed a sheep's heart and measured the content of the ventricle. And now occurs the first application of Galileo's principle of measurement to modern Physiology, an application which makes the study of physiology an orderly body of knowledge. The sheep's ventricle, about the same size as man's, holds 2 ounces. The heart beats 72 times a minute. Therefore, in an hour, the heart pumps into the system 2 x 72 x 60 = 8640 oz. = 540 lbs.; that is, three to four times the weight of the body. Where does it come from and where does it go?

In Harvey's monograph: "Exercitatio de motu cordis et sanguinis in animalibus" the answer appears: "It has been shown by reason and experiment that blood by the beat of the ventricles flows through the lungs and heart and is pumped to the whole body. There it passes through pores in the flesh into the veins through which it returns from the periphery everywhere to the centre, from the smaller veins into the larger ones, finally coming to the vena cava and right auricle. This occurs in such an amount, with such an outflow through the arteries, and such a reflux through the veins, that it cannot be supplied by the food consumed. It is also much more than is needed for nutrition. It must, therefore, be concluded that the blood in the animal body moves around in a circle continuously, and that the action or function of the heart is to accomplish this by pumping. This is the only reason for the motion and beat of the heart."

The weakest link in his chain of reasoning was the lack of demonstration of a capillary transfer. That such a transfer from artery to vein existed was his correct and logical inference. The proof, however, had to wait for the microscope and Malpighi. Such was the great and revolutionary synthesis of painstaking observation of biological data. It was the application of physical methods to the understanding of the body and this application has been repeatedly fruitful. One must remember, however, that such physiology is based on the assumption that the animal body is a mechanical model. This may give a clear image interpreted in mathematical formulae, but does not give the complete truth. A machine is made up of the sum of its parts. An animal body, like a work of art, is greater than the sum of its parts, as Aristotle perceived. The modern philosopher will do well to keep this point of view constantly before the biologists.

William Harvey's great book marks one of the watersheds of man's development. Perhaps only the "Fabrica" of Vesalius disputes its claim to be the greatest of medical books. The work of Harvey opened the way for the exploration into the various physiological functions; in surgery, the improved understanding of the mechanics of circulation was fundamental to advance; in obstetrics, it led the way in 1667 to Needham's demonstration of placental function.

Harvey's work met with much sceptical criticism from his contemporaries. He is quoted as saying: "I not only fear injury to myself from the envy of a few, but I tremble lest I have mankind as my enemy". Largely, however, due to younger men, he enjoyed the universal acknowledgment of his contribution to science for at least twenty-five years before his death.

The other events in Harvey's life are soon told. He became popular in London society, and in 1623, was appointed physician to the King, Charles I. A loyal adherent of the Stuarts, he attended the Lord Chancellor, Francis Bacon, was made a member of the Royal College of Physicians and Surgeons, and lived an elegant and conventional life until the civil war broke out. He remained loyal to Charles, and attended him at the battle of Edgehill. The Roundheads ransacked his London house and seized and destroyed many of his papers. The home of Harvey shared this desecration with many a cathedral. His old age was embittered. He refused the Presidency of the Royal College of Physicians on the basis of his years. A childless widower, he had been robbed of his King and all the sparkling society that had crowded the foot of the Stuart throne. Six years before his death and to his complete indifference, was published his work on embryology: "De Generatione animalium". In 1649, Charles Stuart was beheaded. It is probable that Harvey could not reconcile himself to an England without a King, or to the strange usurper, Cromwell. To Harvey, it appeared that religious fanatics had destroyed his country. "The state is agitated with storms and I myself am at sea in an open boat" were among his last words.

The end come on the third of June, 1657. With the setting sun and surrounded by grieving relatives and friends, the life went out of William Harvey, one of the greatest citizens of our Western world.

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ABSTRACTS

PSYCHIATRY

A Clinical Appraisal of Frontal Lobotomy in the Treatment of the Psychoses, J. L. Hoffman, Psychiatry, 13: 355, 1950.

The author evaluates the results of frontal lobotomy performed on 70 chronic schizophrenics, ranging from 24 to 71 years of age. The median figure for duration of illness is just under 5 years. Prior to lobotomy these patients are overactive, aggressive, assaultive, homicidal and suicidal. They give evidence of being harassed and tortured by their hullucinations and delusions. Their speech is vituperative, angry and profane. They show a limited attention-span, and cannot participate in any form of activity.

There are 2 deaths directly attributable to surgery. Following lobotomy, the patients under observation are found to be listless, withdrawn, inaccessible, irresponsible and childish. They are careless in dress and eating habits, and gain tremendously in weight (80 lbs in one case). They show profound inertia, seldom offer complaints or make requests, and their interest in the milieu in which they find themselves ranges from indifference to complete detachment.

The author follows many of the patients discharged from mental hospital and comes to the conclusion that although there is a marked alteration in the former aggressive character and personality, the schizophrenic now shows even further reduced social adaptability. The relatives of the patient regard his new tranquility and meekness as a miraculous cure. The author, on the other hand, feels that a more natural form of subdued behaviour could be obtained by competent psychotherapy, difficult though it is in these chronic psychoses. Psychosurgery represents a relatively simple technique; and it forever deprives the patient of the possibility of benefit by psychotherapy. Lobotomy should be used as a last resort, after all other available treatment has been tried and failed. At present, there are only three indications for lobotomy:

(1) Where the patient is so agitated that his life or the life of others, is endangered;

(2) where the presence of the patient in the home is vitally necessary to the health and happiness of a parent or spouse;

(3) where the hospital, and its staff, are prepared and qualified to make a truly scientific study of the indications for, results of, and possible modification of frontal lobotomy.

G. J. Halpern

Effect of Glutamic acid on Mental Function: Pilot Study, William J. Kerr and S. A. Szureli, Paediatrics, 5: April, 1950.

The administration of large doses of levo glutamic acid to children of normal intelligence produced no significant change in testable intelligence as compared receiving a placebo (glycine-2-tartaric acid).

The results do not substantiate previous reports that glutamic acid will increase measurable intelligence. Attitudinal effect on the part of nurses, psychologists and psychotherapists which might have influenced the results, was minimized by the use of careful controls and different psychologists in each test situation.

Because of the small number of cases reported, further studies are needed on larger groups with similar controls. A hospital with a large stable population of children with low testable intelligence would be preferable to the Langley Porter Clinic. One such study is soon to be reported. The results are essentially in agreement with those of the authors.

I. Eisen

Emotional Problems of High Blood Pressure, Weiss, Jaffe, and Fischer, Amer. J. of Psych., 107: No. 4, 1950.

An attempt is made to present the psychosomatic approach to the study and treatment of hypertension. The early symptoms of hypertension are frequently exactly those of a psychoneurosis, and emotional stress often seems to precede

the onset of hypertension. Too much importance has been attached to the "physical" treatment of bringing the blood pressure down and this has only added to the phobia of high blood pressure.

In dealing with hypertensive patients it is well to explain, that inner tension which cannot be released through action, words, or other channels, may manifest itself in the circulatory system through the changes known as hypertension. A combined physical and psychological study of the patient is necessary. In many patients the emotional component is very important in the production of symptoms, as head-ache, vertigo, cardiac neurosis. Hypertension seems to occur most frequently in people with compulsive characters, and inhibited aggression may bear a relationship to high blood pressure. The blood pressure may or may not be affected by psychotherapy, but anxiety is often diminished and the patient may be subjectively improved.

R. V. Speck

OBSTETRICS

Symposium on Estrogenic Hormone Imbalance and Uterine Cancer, L. A. Enge, West. J. of Surg. Obst. and Gyn., **58**: 490, 1950.

The author states that in man cancer of the genito-mammary components has been discovered in the course of protracted estrogen therapy. Further, it is the free or unmetabolized estrogens which provoke genital and mammary hyperplasia, and this hyperplasia under continued estrogen stimulation will progress to cancer. The circulating estrogens become free or unmetabolized due to a vitamin B deficiency of the liver, preventing inactivation of these substances.

H. Axelrod

The Management of Threatened Abortion; A Study of 100 cases, Commander R. E. Drawder et al, Amer. J. of Obst. and Gyn., **60**: No. 4, 1950.

One hundred cases of threatened obortion are reviewed in an attempt to evaluate the efficacy of stilbestrol in the management of threatened abortion. Threatened abortion is defined as the occurence of uterine bleeding with or without uterine cramps in a uterine pregnancy of less than twenty weeks gestation.

Each patient was admitted to hospital on one of two treatment routines in order of admission.

1) a. Bed rest until symptomless for 24 hours.
   b. Phenobarbital 0.1 Gm three times daily until asymptomatic for 24 hours.
   c. Demerol or Pantopon, 100 mg. on admission and 50 mg. every four hours until cramping had ceased.
2) a. Bed rest and sedation as in Routine 1.
   b. Diethylstilbestrol 25 mg. every 30 minutes for 6 doses then 100 mg. daily until asymptomatic for 24 hours then 50 mg. daily to the 28th week of pregnancy.

Results of Treatment

On Routine 1,57% retained their pregnancies. Each of these maintained her pregnancy to viability.

In recent literature many articles have recommended the use of either progesterone or stilbestrol in the treatment of threatened abortion.

The administration of progesterone theoretically helps to maintain the blood level of progesterone at the time when the syncytium of the chorionic villi is begining to take over the secretion of progesterone from the degenerating corpus luteum. The progesterone will inhibit uterine contractions, thus helping to maintain the pregnancy. But Davis and Fugo showed that in most pregnancies threatening to abort, the excretion of sodium pregnandiol glucuronate in the urine was normal, indicating no lack of progesterone. Stilbestrol is claimed to be of value by increasing the production of progesterone, probably the placental syncytium, as a result of increased utilization of chorionic gonadotrophin. But patients receiving large amounts of stilbestrol do not show an increased level of pregnandiol excretion. The use of stilbestrol in threatened abortion has therefore no theoretical basis. The authors conclude from the results of their study that stilbestrol is of no value in the treatment of abortion.

S. P. Starkman

PATHOLOGY

Multiple Myeloma: Lesions of the Extra-osseous Hematopoietic System, Jacob Churg and Alvin J. Gordon, Amer. J. of Clin. Path., **20**: 934, 1950.

These authors state that the occurence of extra-medullary myelomatous lesions in cases of multiple myeloma is the rule rather than the exception, as has previously been believed. They base their conclusion on a review of 30 cases of multiple myeloma occuring between 1933 and 1948 which were found among 5400 post-mortem autopsies at Mount Sinai Hospital in New York. In 22 of the 30 cases (73%) involvement of extra-skeletal hematopoietic tissues (lymph nodes, spleen, and liver) was definitely established; in 10 of these cases there was gross evidence of nodular infiltration. The identification of extra-skeletal lesions as being myelomatous was achieved by comparing the microscopic picture to that found in the bone marrow of the same patient whenever "typical myeloma cells" were difficult to distinguish in the extra-skeletal sites.

A full discussion and description of the lesions found in the spleen, liver, and lymph nodes is given, illustrated by thirteen photomicrographs. In 9 of the cases myelomatous infiltration of organs other than the three mentioned above was found; the kidney being most frequently involved (7 out of the 9 cases).

The article concludes with a classification of extra-medullary lesions (1) those with only vascular infiltration, (2) those with diffuse myelomatous infiltration, and (3) those with discrete nodular formation; the diffuse type was found to be most common. The histogenesis of the myeloma cell is also discussed. The authors agree with Bayrd that the myeloma cell is derived from the primitive reticulum cell which becomes converted into a large or small stem cell, and disagree with Lowenhaupt's theory that it is derived from the endothelial lining of the splenic sinusoids.

Addendum

In 14 additional cases of multiple myeloma discovered at autopsy since the writing of the article, 9 showed myelomatous infiltration of lymph nodes, liver, and spleen. Thus in the entire series of 44 cases involvement of the extra-osseous hematopoietic system was found in 31 (70%).

G. W. Shepherd

The Pathology of Hyperpyrexia, Ira Gore and Capt. Norman Isaacson; Amer. J. of Path., **25**: 1029, 1949.

Heat in various forms is one of the oldest of therapeutic agents, although until recently was employed only by local application. Probably the first planned attempt to utilize increased body temperature as a therapeutic measure was made by Wagner von Jauregg in the malarial treatment of paresis. Typhoid vaccine and other biologic substances have been used since, and various mechanical and electrical devices have been constructed to serve the same purpose. Therapeutic hyperpyrexia has become an established means of treatment, not only for paresia, but for various forms of arthritis, chorea, asthma, sulfa-resistant gonorrhea and other diseases. As a consequence of its widespread adoption, numerous studies of the physiologic changes accompanying hyperpyrexia were undertaken.

In this article seventeen fatal cases of therapeutic hyperpyrexia have been reviewed to ascertain the nature of any pathologic changes that might have occurred. The underlying disease in each instance was of a type not usually associated with more than local tissue changes. Therefore, except for certain complicating factors considered in the text, morphologic alterations were regarded as the result of the controlled fever.

Congestion and purpuric haemorrhages were the rule. Patients who did not die within 48 hours after the fever also exhibited jaundice. Microscopically, necrosis of cells and other degenerative changes were observed in the brain, heart, liver, kidney, adrenal glands and testes. The alterations, especially in the liver, were progressively more severe as the survival time increased. It is inferred that the absence of visible change when death is prompt merely expresses the limitations of current histologic technique.

Anoxia and deleterious effects of elevated temperature upon essential cellular

enzymes and enzymic reactions are probably the chief factors in producing these pathologic effects. Fever in many conditions besides pyretotherapy may produce similar lesions.

H. M. P. Ives

MEDICINE

Relation of Nutritional Deficiency in Man and Antibody Production, Henry H. Balch, Jour. of Immun. **64**: 397-410, 1950.

The test group in this investigation consisted of 25 nutritionally depleted patients whose history showed a recent weight loss due to inadequate diet or some pathological disorder. The control group on the other hand, consisted of nineteen individuals (hospital staff or patients) who had maintained a constant weight for a period of one-half a year before this study was undertaken. This investigator used purified diphtheria toxoid as the antigen, and the anti-toxin production following a single intramuscular dose of this toxoid was measured quantitatively. All the individuals concerned in the test were Schick negative so that the response to the antigen would be more marked.

The conclusions drawn from this investigation were as follows:

(1) No relation was found to exist between the antibody response and total serum protien, serum albumen or *serum globulin* levels. (The measurements of gamma-globulin levels was not possible to determine during these investigations.)

(2) Severely ill, nutritionally depleted patients were found capable of producing antibody, as well as, or better than the healthy controls. Furthermore, antibody production was found to continue up to the time of death from a wasting disease.

(3) No relation was found to exist between antibody response and the age of the patients.

(4) The initial anti-body level of the individual had no effect on the antibody response.

(5) No relation was found to exist between antibody response and the development of infection.

S. Davis

Smoking and Carcinoma of the Lung, Richard Doll and A. Bradford Hill, B.M.J., September, 1950.

This article is an investigation into the possible association of carcinoma of the lung with smoking, by using material obtained from 20 hospitals in the London area. 739 cases of carcinoma of the lung were interviewed as to their smoking habits and for a control 739 non-cancer cases were interviewed at the same time in the same hospital.

A smoker was defined by the authors as one who smoked as much as one cigarette a day for as long as a year. Smoking habits were divided as follows; (1) non smoker (2) 1 cigarette per day (3) 5 cigarettes per day (4) 15 cigarettes per day (5) 25 cigarettes per day (6) 50 or more cigarettes per day. 0.3% of lung cancer patients were classified as non-smokers by the above definition. 4.2% of non-lung cancer patients were non-smokers. 26.0% of lung cancer patients smoked 25 or more cigarettes per day as compared with 13.5% in the control group.

Cigarette smoking was more closely related to cancer of the lung than was pipe smoking. Inhaling made no significant difference. Lung cancer patients on the whole began to smoke earlier and continued longer than did the control cases.

This article is a carefully written accurate piece of statistical analysis of a large series of cases of carcinoma of the lung. Every precaution has been taken to prevent errors from affecting the results of the survey.

The authors come to the conclusion that carcinoma of the lung is definitely related to the habit of smoking tobacco.

E. L. Masson

Diabetic Retinopathy, J. S. Friedenwald, Amer. J. of Ophth. **33**: No. 8, 1950.

Diabetic retinopathy has a pathology all its own. Its characteristic "deep retinal hemorrhages" which are usually spherical, about thirty microns in diameter and surrounded by a cluster of exudates, have been shown to be capillary aneurisms in flat stained retinal preparations. As with aneurisms of the base of the brain these occur at bifurcations or sharp bends in the

capillaries. They are not the result of increased venous pressure since they are seldom found in occlusion of the central vein. These so-called "deep retinal hemorrhages" are present for months not being absorbed in a few days as are true retinal hemorrhages and exudates. Their duration and appearance are diagnostic features of diabetic retinopathy.

It is interesting to note that, first, diabetic retinopathy bears no relation to ophthalmoscopic retinal arteriosclerosis; second, the number of hemorrhages bears some relation to the state of capillary fragility, and third, (in diabetics), there is a high co-relation between intercapillary glomerulo-sclerosis as described by Kimmelstiel and Wilson, and diabetic retinopathy. Twenty-five showed evidence of intercapillary glomerulo-sclerosis, and in thirty-three diabetics without retinopathy no cases showed evidence of intercapillary glomerulo-sclerosis. In both these conditions there is a hyaline thickening contiguous with the basement membrane of the capillaries. However the hyaline deposits in the glomeruli are not analogous to the waxy retinal exudates.

While the relationship between the clinical and pathological findings appear to be reasonably clear, the relationship between the pathological and biochemical findings remains in the dreamy realm of theory. However it does seem likely that the hyaline deposits found in the renal and retinal lesions mentioned above are related to complex changes in the metabolism of the muco-polysaccharides rather than to simple hyper-glycemia.

In summary—diabetic retinopathy is specifically related to diabetes; differs from arteriosclerotic retinopathy; is not produced by occlusion of the central vein, and is believed to be related to intercapillary glomerulosclerosis but its pathogenesis is uncertain.

P. Beacock

Abuse of Bed Rest in Myocardial Infarction, C. Warren Irvine Jr. and Alexander M. Burges Jr., New Eng. J. of Med., 486, September, 1950.

The authors suggest that since death from rupture of the heart and from occurence of arrhythmias occur mainly in the first two weeks after cardiac infarction, that activity after this time is not contraindicated. Hypostatic pneumonia, atelectasis, constipation, phlebothrombosis and embolism, and psychological upset as a result of prolonged bed rest are indications for early restoration to activity.

They reason that 2 weeks in bed, with reasonable, carefully explained instructions and possibly bedside toilet privileges with discharge from hospital at the end of four weeks, are all that is necessary in the majority of cases.

D. A. Smith

Pulmonary Arterio-Venous Aneurysm, G. E. Lindskog, A. Liebon, H. Kansel, A. Janzen, Annals of Surgery, 132: No. 4, 1950.

The patient complains of cyanosis and clubbing, usually since childhood, C.N.S. symptoms of headache, vertigo, dizziness referable to the polycythaemia and occasionally chest discomfort, weakness, lassitude and weight loss. Epistaxis is common.

Physical examination shows the heart to be normal and the spleen unenlarged. There may be a rough and continuous murmur over the site of the pulmonary lesion. 50% of patients show spider telangiectasia or nodular cutaneous hemangiomas.

This latter finding suggests the nature of the lesion to be a developmental anomaly related to hereditary hemorrhagic telangiectasia.

Chest X-ray shows a clustered homogeneous density and enlarged tributary vascular channels which may be more clearly visualized by laminography or angiocardiography.

Treatment is lobectomy, pneumonectomy or local dissection for bilateral multilobar lesions.

D. Horan

Primary Complex of Tuberculosis, Alfred D. Biggs, Amer. J. of Dis. of Children, 80: No. 4, 1950.

In an attempt to clarify clinical and roentgen conceptions of primary tuberculosis this author studied a group of 142 children over one year of age with a positive tuberculin test. These patients were followed by careful clinical examination,

laboratory investigation, and serial roentgenograms (more than half were followed for 5 years.)

None of the groups with ordinary primary infection had fever cough or rales not explained by some co-existent disease or retardation in height or weight growth. Blood findings were all within the normal range except for an increase in sedimentation rate in 13% of cases and gastric washings were negative for tubercle bacilli.

The primary complex is diagnosed by a postive skin test and a slowly changing roentgen shadow. Shortly after the skin test becomes positive, soft diffuse shadows appear in one or more lobes and within a few weeks the hilar shadows become enlarged. In two or three years the peripheral markings become inconspicuous linear shadows. Calcium deposition (beginning in 2 years and continuing for 1 to 3 years more) occurs in the peripheral lesions in only 25% of cases (true Ghon tubercle) while it is present in the contracted hilar lesions in over 90% of cases.

Only three cases of massive primary complex (epituberculosis) were seen during the 8 years of this study and these children had mild symptoms, showed large conspicuous shadows involving one lobe of the lung, and had laboratory confirmation of tuberculosis.

Children with ordinary primary tuberculosis were removed from the source of infection, but no other treatment was given. Those patients with massive primary infections were isolated and treated symptomatically.

R. S. Fowler

Observations on the Prolonged Medical Management of Toxic Diffuse Goiter with Thiouracil and Propylthiouracil, S. U. Greenberg and M. Bruger, Amer. J. of Med. Sciences, **943**: 373-380, 1950.

A five year study on the prolonged treatment of thyrotoxicosis in 70 patients by propylthiouracil is presented with observations on: (a) remissions and relapses; (b) exophthalmos; (c) changes in the size of the thyroid gland.

Medical treatment was advised because (a) operation was refused; (b) presence of medical complications increasing surgical risk; (c) thyroid resection had been done and further surgery was inadvisable; (d) cases of mild hyperthyroidism. Adequate treatment was considered to consist of doses sufficient to lower the B.M.R. to a negative reading, and to maintain it there for one year. In this series they first used thiouracil, switching to propylthiouracil when it became available. Average initial doses of the latter were 300 mg. per day, and maintenance doses, 50 - 100 mg. per day. A remission persisting for six months was considered satisfactory.

Results show that of 39 cases receiving adequate treatment and follow-up, 77% had remissions for six months, and 64% for over one year. 15 similar cases did not receive adequate treatment because of toxic symptoms in 9 (mostly on thiouracil) and lack of co-operation in 6. A further 17 patients are still under treatment. 12 of these patients have received prolonged treatment for from 1 - 3 years giving satisfactory control with no complications. They further conclude that if remission lasts for 6 months then the chance of relapse is small, and if it lasts for one year then the chance of relapse is remote. They believe the fewer remissions reported in other series to be due to inadequate treatment. In only three cases did the drug have to be discontinued due to toxicity. In their early relapses they noted a surprising sex incidence, 4 relapses occured in 5 males treated, and 5 relapses in 34 females treated.

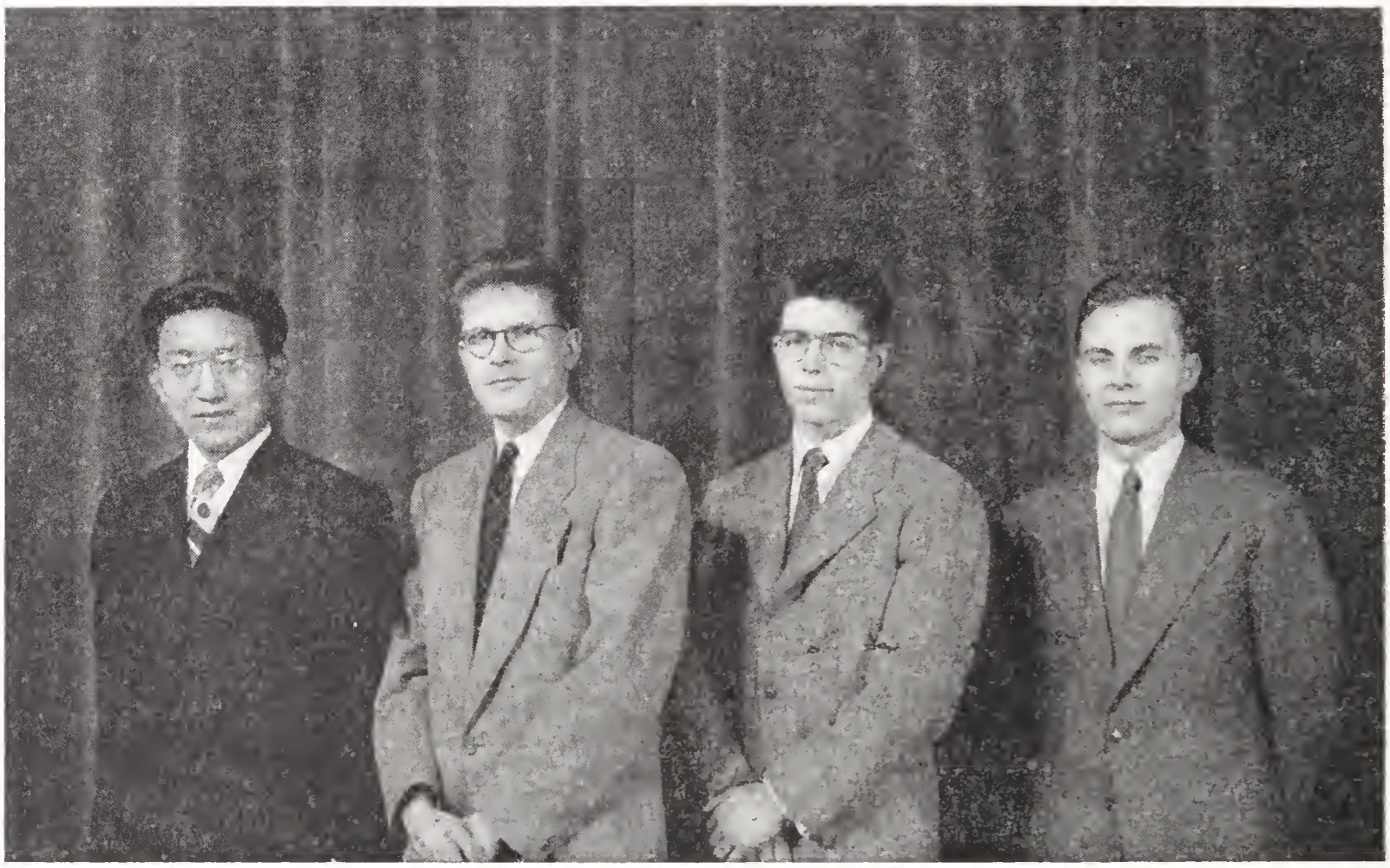
Exophthalmos was noted in 18 cases. Of these 9, or 50%, showed regression, 9 showed no change under propylthiouracil, though two of these showed an increase following thyroidectomy.

Study of gland size under medical treatment showed that of 27 patients, 13, or 48%, got regression of the gland; 12, or 45%, remained unchanged, and in only 2 (7%) cases did the gland enlarge, and without pressure symptoms.

They also noted that in cases of granulocytopenia, pyridoxine hydrochloride orally in doses of 60 - 150 mg. daily, appeared to act as a granulocytic stimulant.

J. McIntyre

NEWS AND NOTES



MEDICAL ALUMNI SCHOLARSHIP WINNERS
G. Y. Hiraki, W. D. Friend, C. D. Anderson, D. A. Smith

Medical Society

Students of the Medical Faculty are rallying behind the All Varsity Aid organization in its endevour to assist students in South-East Asia. The plan calls for the adoption of the universities of Sindh in Pakistan and Jamia Millia Islamia at New Delhi, India. The Faculty of Medicine is prominently represented on the executive. This committee is headed by Vice President Syd Wax and George Morrison, as Vice Chairman, is representing NFCUS.

* * *

The annual Faculty show, "Daffydil" which is scheduled to be held in the Hart House Theatre from December 11 - 14, is out of the blue print stage and on to the rehearsal stage. Chairman Bill Monk and Director Sam Bogoch head a talented team of medical entertainers for the production of this high-lighted show. They have promised a more compact show with year skits, dance routines and other special features. The problem of equitable ticket distribution has been solved by the adoption of a faculty wide scheme to alleviate this condition.

* * *

The Medical Arts and Letters Club was initiated this year with a lecture by Dr. Alan Bruce-Robertson. The lecture, illustrated by colored movies, dealt with the speaker's work in Alaska and the Yukon with the Artic Institute of America. The Rev. Herbert Leggate addressed the Club on Thursday, November sixteenth. He chose as his topic, "Youth in the Changing World".

The extablishment of a Debating Society is the most recent accomplishment of the Arts and Letters Society. This organization, under the chairmanship of R. W. Shepard plans to stimulate student interest in topics of current affairs and freqquent informal meetings are sheduled for the coming year.

The Medical Glee Club, which is now a subsidiary of the Arts and Letters Club,

is meeting every Thursday at five o'clock in the Anatomy Lecture room. Musical Director Clayton Rose and his group were featured at the Medsmen's All Varsity Dance, "Panacea" in a selection of special musical arrangements.

The appointment of Dr. M. H. Brown as Honorary Chairman of the Arts and Letters Club has been announced.

* * *

The Medical Year Book *Palinodia,* after making its successful debut last year, promises to be bigger and better than ever this year. This Torontonensis in miniature will feature a completely new and different format, improved individual pictures of all undergraduates and a complete review of the years' medical activities. Supporting the editor, J. A. McDonald, in this mammoth task are J. W. Goodwin, managing editor, R. Wilson, business manager and J. B. Sullivan, news editor.

Camsi

The fourteenth annual Conference of CAMSI was held at the University of Montreal from October twentieth to twenty-second inclusive. Bruce Buchanan and Abe Halpern represented the University of Toronto at the convention, and their report is indicative of a productive and successful meeting. The officers for the National Executive are members of Queen's University.

The CAMSI Journal, under a spirited editorial staff, have planned certain improvements for this year's issue. There will be changes in the cover, quality of paper and size. The contents will be expanded to include diagnostic problems, medical crossword puzzles and more but briefer abstracts. More advertising is hoped for in order to keep the costs of production down. The University of Toronto is responsible for the publication of the January edition.

The program for National CAMSI during the coming year includes the continuation of the Medical Film service and the establishment of a permanent secretariat. Continued work is hoped to produce more benefits for Canadian medical students in securing summer employment and interne placement. American students have shown much interest in the Canadian Interne Placement Service and they will institute a plan based on it next year.

CAMSI is now affiliated with the British Medical Students Association, and plans for student or interne exchange are being investigated.

Each year Awards are made in conjunction with the National Convention. R. S. Angus, Meds 5T2, received second prize and honourable mention in the photographic exhibit at the Art Salon. The University of Toronto Medical Journal won the CAMSI prize for the best undergraduate medical journal in Canada.

* * *

Athletics

The Medical Athletic Association has had a successful autumn season. Soccer, lacrosse and volley-ball teams deserve special commendations for their achievements. Hockey and basketball are just getting under way, but the Faculty is already watching with interest the progress of Medical teams in these loops. Medsmen were well represented on the Senior Varsity Blues foot-ball team this year. Carrying the fight for the Blue and White were: Tony Ceccutti, John Evans, Harry Hyde, Don Longmore, Jim Murray, J. F. (Moose) Mustard, Doug Shay and Doug Wigle.

Dr. W. Dafoe, a member of the University of Toronto Athletic Derectorate and donor of the Dafoe Cup for inter-faculty lacrosse, has been appointed Honorary chairman of the M.A.A.

The M.W.A.A. reports that the girls baseball team, unbeaten to date, has reached the semi-finals. The basketball season is just beginning but the girls have won all their games so far and they look forward to the playoffs with high hopes and confidence.

* * *

The Annual Medical Womens Undergraduate Association Banquet in honour of the new members was held on October the seventeenth at Chez Paris. Dr. Agnes Jamieson was guest speaker. Her topic on General Practice was enthusiastically received by everyone. Plans are being made for the M.W.U.A. christmas party to be held on December the nineteenth at the School of Nursing.

* * *

The announcement has been made of recent undergraduate scholarship winners. Mr. J. M. Johnson, Meds 5T6, has received the Medical Alumni Admission Scholarship valued at two hudred dollars; Miss R. Ubriaco, Meds 5T6, has been awarded the Samuel Godfrey Scholarship; The Famous Canadian Corporation Scholarship of five hundred dollars has been won by Mr. H. P. Brent, Meds 5T4; Mr. R. B. Speck, Meds 5T1, has received the Phi Delta Epsilon Fraternity Bursary in Obstetrics and Gynaecology.

* * *

Dean MacFarlane has announced that the University of Oxford has offered a scholarship in that university to a student from Canada beginning in the academic year 1951-52. The scholarship will be worth approximately £350 annually and may be held for five years. Eligibility for the scholarship may be satisfied by Physiology and Biochemistry graduates on completion of the first medical year, first year students in medicine who have completed their physiology and second year students. Details are available in the Deans office.

FACULTY

Health Minister MacKinnon Phillips states that medical resources of the University of Toronto are to be brought to bear by the Ontario Government for research and demonstration program on alcoholism and its treatment. A central clinic will be established in Toronto, Dr. Phillips says, screening incoming patients, giving some treatment and sending others to one of three Toronto teaching hospitals or to the provincial hospital of alcoholism now nearing completion at Erindale. Plans for the future call for courses of lectures at universities both for graduates and undergraduates in medicine, psychiatry and sociology dealing with problems related to Alcoholism.

* * *

An eye bacteriology laboratory under the direction of Dr. H. L. Ormsby has been started at the Banting Institute in the Dept. of Ophthalmology. Ophthalmologists may refer their private cases to the laboratory for bacteriological investigation.

A tonometer testing station has been established at the University as a service to the Ophthalmologists of this country with funds provided by the federal government. Oculists who know or suspect that the readings of their tonometers are faulty are requested to forward their instruments to the Tonometer Testing Station, Rm, 82, Banting Institute, Toronto.

* * *

The appointment of Dr. R. M. Wansbrough as Chief surgeon of the Hospital for Sick Children has been announced by R. A. Laidlaw, chairman of the board of governors. Dr. Wansbrough, a graduate of the University of Toronto in 1924, joined the surgical staff of the Hospital for Sick Children in 1929. He served with the Canadian Army overseas, during the last war.

* * *

The Professor of Medicine, Dr. R. F. Farquharson, is the author of a recently published book by Charles E. Thomas, entitled, Simmonds Disease—Extreme Insufficiency of the Adenohypophysis.

* * *

Dr. William Boyd, professor of Pathology, will be in Houston, Texas from November 20 to 22 where he will deliver a series of Lectures to the Post Graduate Medical Assembly of South Texas.

* * *

Dr. W. G. Bigelow and Dr. J C. Callaghan have recently presented a paper before the American College of Surgeons in Boston on experimental work dealing with the problem of cardiac standstill. Both Dr. Bigelow and Dr. Callaghan are on the staff in Surgery. Their machine, called the Artificial Electric Pacemaker, is expected to find useful application in cases of serious cardiac arrest.

* * *

Dr. Hammet A. Dixon has been appointed associate professor of Dermatology.

* * *

Visitors to the university during November included Dr. J. P. Bull, Burns Unit, Medical Research Council, Birmingham University and Mr. Alastair Wallace, Dept. of Surgery, Edinburgh University.

A. M. ROBERTSHAW

PIONEER MEAT EATER

(5 years later)

Bill Purvy at one year. He became a participant in Swift's first meat-feeding test at 4½ months.

Current Clinical Meat Feeding Studies

REPORT No. 4

EFFECT OF MEAT IN THE DIET OF INFANTS AND YOUNG CHILDREN

Results of this study indicate that meat promotes hemoglobin and erythrocyte formation. These findings were revealed in a preliminary report published in the J.A.M.A. (134 1215 (1947). The present studies are a continuation of the work reported in this article.

This study is part of an extensive clinical research program now being conducted through grants-in-aid made by Swift's.

Long before Swift's Meats for Babies were available generally, little Bill Purvy was eating them every day. He started at 4½ months. That was over five years ago—during Swift's original meat-feeding tests. Before the development of Swift's Meats for Babies, the customary age to start meat was at least *six* or *nine* months. And because home preparation was so complicated, most babies simply did without!

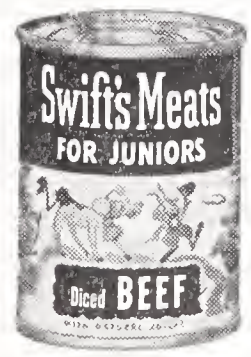
"He's a healthy boy"

Says Bill's mother, and it's evident from the picture of Bill above. His mother reports that he liked Swift's Meats for Babies from the beginning.

Today any baby can have the same right start in life that Bill had. Doctors now recommend Swift's Meats for Babies in the early weeks of life — to provide the complete, high-quality proteins and iron every infant needs every day.

Swift's appetizing variety includes: beef, lamb, pork, veal, liver and heart—to help infants acquire a taste for variety and form sound eating habits.

Swift's Meats for Babies are trimmed and cooked expertly—to minimize fat content and preserve a maximum of nutrients: They're convenient—ready to serve!



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...first to develop and clinically test 100% Meats for Babies

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Your patients will be pleased when you prescribe Rheumatol E.B.S. because of its soothing anodyne effect.

INDICATIONS:

Rheumatol is a stimulating local application in muscular pains, neuralgia, sciatica, lumbago, sprains and bruises.

CONTAINS:

Camphor, Menthol, Chloral Hydrate 1%, Essential Oil of Mustard and Methyl Salicylate.

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RHEUMATOL E.B.S.

is packaged in two and four ounce bottles and in pounds, winchesters and gallons.

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is packaged in one ounce tubes and one pound jars.

THE *E.B.S.* SHUTTLEWORTH CHEMICAL CO. LTD., TORONTO, CANADA

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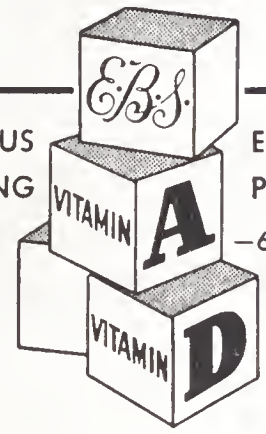
For Your Finicky Patients Prescribe Pleasant Tasting **Rikitol** EMULSION



AN AQUEOUS EMULSION CONTAINING PER GRAM
—60,000 I.U.
—12,000 I.U.

Rikitol Emulsion Provides Greater Absorption Better Storage

CLINICAL EVIDENCE

J. M. Lewis and co-workers(1) gave eight premature infants 35,000 units of Vitamin A, first as an oil solution and later the same dosage as a water emulsion. They found the average rise in Vitamin A concentration in the blood of these infants to be 62 units and 274 units after the oil and the water emulsion respectively.

Sobel et al(2) compared the amounts of the vitamins stored in the liver of rats after it had been given in oil to one group of animals and in aqueous emulsion to another group. They used Vitamin A from three different sources. The results of their experiments showed an average of 160% better storage when the aqueous emulsion was used.

(1) Lewis, Bodansky, Birmingham and Cohlan, J. Pediatrics 31, 496 (1947)
(2) Sobel, E. A. et al, J. Nutrition 35, 225 (1948)

AVAILABILITY:

Rikitol Emulsion E.B.S. is packaged in 4 cc., 15 cc., and 30 cc. dropper bottles. It is given by stirring one or more drops into milk, orange juice, cocoa or other beverage. It is highly flavoured so that upon dilution, it has a pleasant fruity taste.

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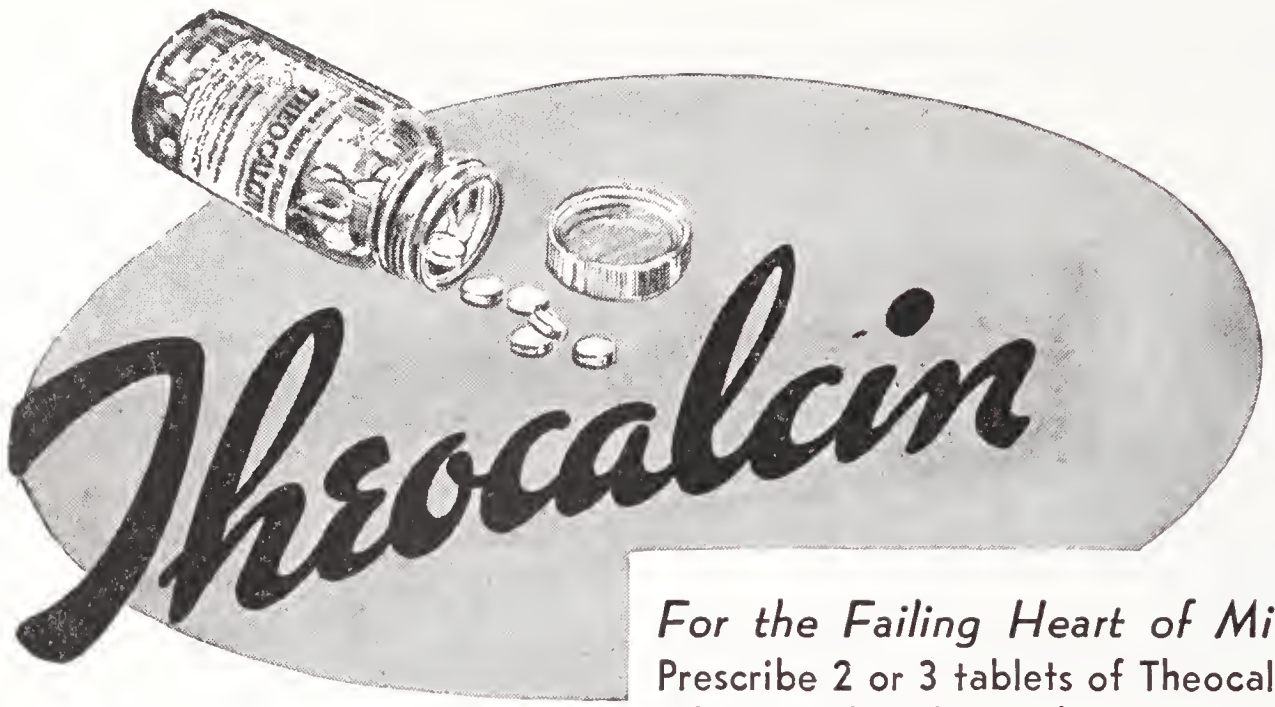

For the Failing Heart of Middle Life

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have developed these products, all of which are rapidly receiving the greatest commendation in Canada, Great Britain, France and the United States for their extreme originality and their donation to medical advancement

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The addition of a new dispersing agent potentiates the spermicidal efficacy of Ortho-Gynol by increasing the dispersability of its active principle. We've been shipping the new Ortho-Gynol for the past several months. Your pharmacist has it now in the same distinctive Ortho-Gynol package.

The most widely prescribed vaginal jelly

Ortho-Gynol Vaginal Jelly—Ricinoleic acid 0.75 % boric acid 3.0 % and oxyquinoline sulphate 0.025 %.

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ACTIVE INGREDIENTS: Dodecaethyleneglycol Monolaurate 5%, Boric Acid 1%, Alcohol 5%

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affords a high degree of protection

Ramses VAGINAL JELLY
is easy to use

Ramses VAGINAL JELLY
doesn't melt or run at body temperature.

"RAMSES"* Vaginal Jelly meets or exceeds all the requirements of the Council on Pharmacy and Chemistry of the American Medical Association.

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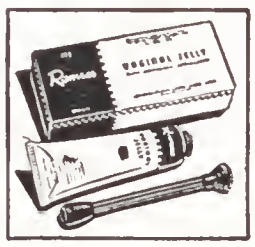

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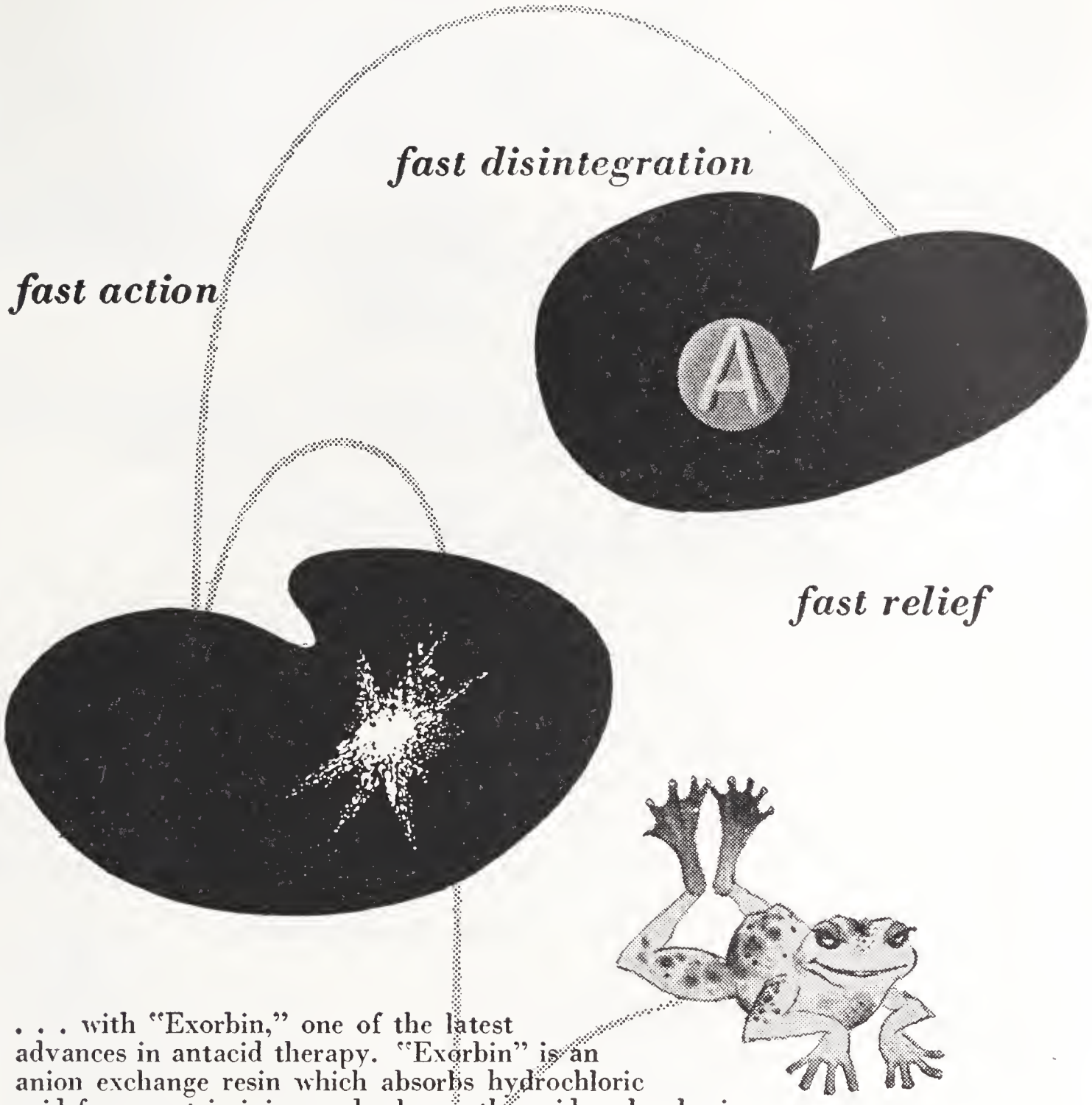

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"Exorbin" (No. 373) in tablets of 0.25 Gm. (4 grains); bottles of 100. Also available in Powder (No. 375) in jars of 2 ounces.

[1]Kraemer, M.: Postgrad. Med. 2:431 (Dec.) 1947.
[2]Kraemer, M., and Siegel, L.H.: Arch. Surg. 56:318 (March) 1948.
[3]Martin, G. J., and Wilkinson, J.: Gastroenterology 6:315 (Apr.) 1946.

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brand of Polyamine Resin

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Vitamin A	500 International Units	Ascorbic Acid	25 milligram
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Each 0.6 cc. supplies:

Vitamin A	5000 Int. units
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Ascorbic Acid	50.0 mg.
Thiamine	1.0 mg.
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Vitamin A	5000 Int. units
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Tutamate aids in the prevention of

- prematurity,
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Principal ingredients	in daily dose
Ferrous sulphate (exsic.)	3 gr.
Copper sulphate	2/25 gr.
Vitamin A	5000 I.U.
Vitamin D	2000 I.U.
Calcium phosphate	4 gr.
Sodium iodide	1/162 gr.
Thiamine HCl	2 mg.
Riboflavin	3 mg.
Pyridoxine HCl	1 mg.
Calcium *d*-pantothenate	5 mg.
Niacinamide	10 mg.
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Mixed tocopherols	12 mg.

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2 capsules daily, or more as required.

MODES OF ISSUE

Boxes of 50, 100 and 250 capsules.

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THE SYMBOL OF PROGRESS
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Brand of vitamin B compound with vitamins C and D

For the treatment of
VITAMIN DEFICIENCY STATES

Beforte is recommended for the correction of dietary deficiency, and provides a useful adjunct to treatment during the acute or recuperative stages of disease. Diets in the following circumstances are actually or potentially deficient in vitamins and should, therefore, be supplemented:

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For the prophylaxis of radiation sickness, Beforte Tablets should be started 3 or 4 days before radiation is begun, and continued throughout the entire course of treatment.

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S.C.T. No. 360 "Frosst"

Each tablet contains:

Brewer's yeast concentrate	150 mg.
Thiamine HCl	3 mg.
Riboflavin	2 mg.
Niacinamide	12.5 mg.
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Calcium *d*-pantothenate	5 mg.
Vitamin D	500 I.U.
Ascorbic acid	25 mg.

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One to three tablets daily.

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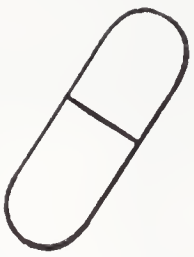

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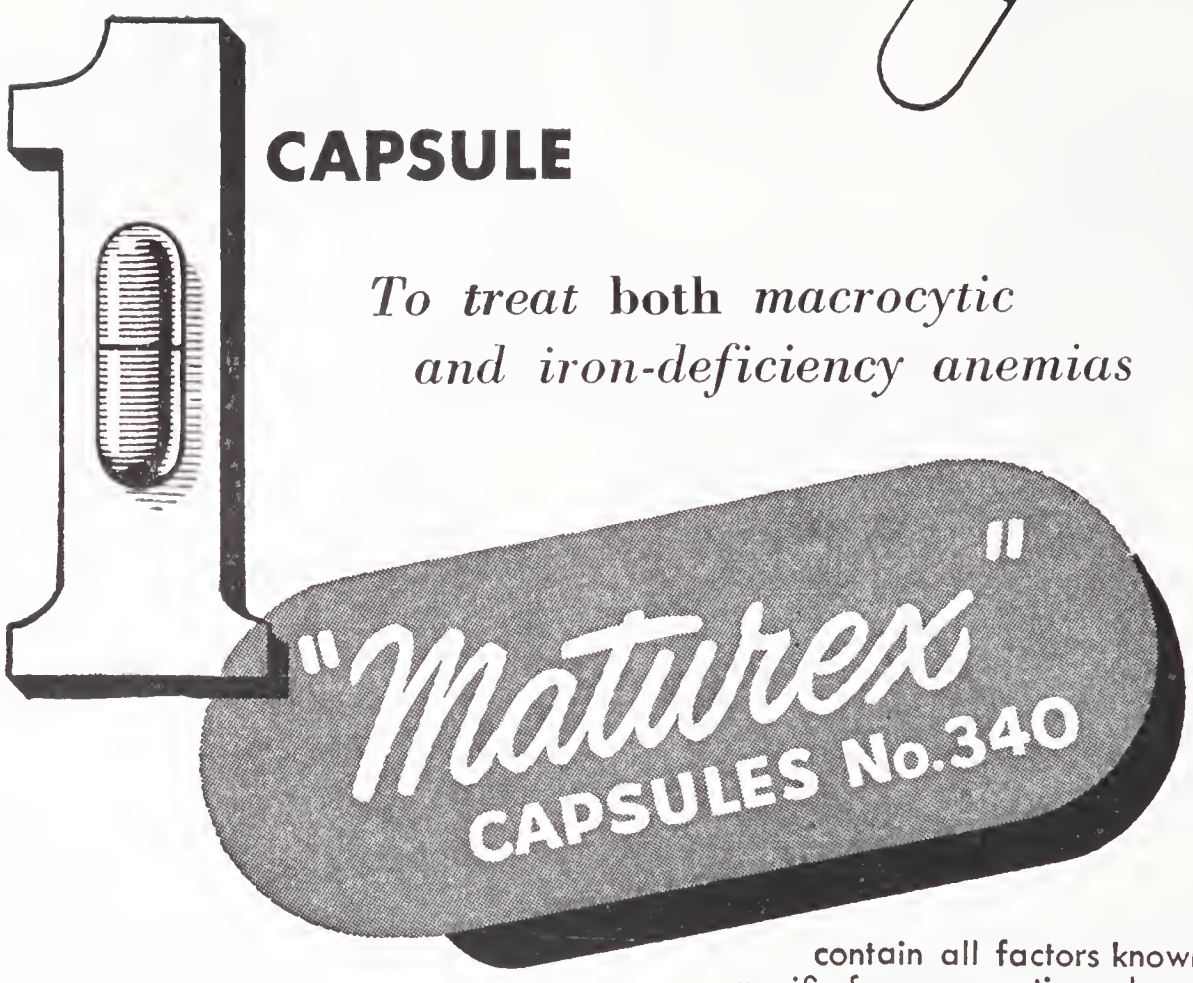
To treat **both** *macrocytic and iron-deficiency anemias*



contain all factors known to be specific for macrocytic and iron-deficiency anemias

Each capsule contains:

Vitamin B_{12}	10 mcgm.
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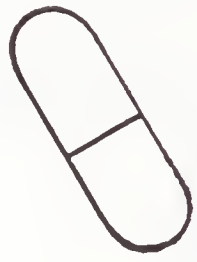
Ascorbic Acid	50 mg.

Supplied in bottles of 100 and 500



"Maturex" Capsules are indicated for the **oral** treatment of hypochromic and hyperchromic anemias, including pernicious anemia, pellagra, sprue, megaloblastic anemia of pregnancy, iron-deficiency anemia, and for retarded growth.

The recommended dosage is one capsule three times daily, to be taken after meals. In pernicious anemia, it may be necessary to increase this dosage in the initial stages, in relapse, or where there is combined degeneration.

AYERST, McKENNA & HARRISON LIMITED

BIOLOGICAL AND PHARMACEUTICAL CHEMISTS

Montreal, Canada

SUPERIOR

PENICILLIN THERAPY WITH

Penicillin S-R

TRADE MARK

Soluble

plus **R**epository *penicillin*

for the physician

faster, higher initial levels... prolonged, high maintenance levels... better control of infection... quickly injected

for the nurse

easily prepared... aqueous diluent... no vigorous shaking... free-flowing in syringe and needle

for the patient

no sensitizing diluents... complete absorption—no wax or oil... minimal pain

Penicillin S-R is supplied in one-dose (400,000 units), five-dose (2,000,000 units) and ten-dose (4,000,000 units) vials. When diluted according to directions, each cc. contains 300,000 units of crystalline procaine penicillin-G and 100,000 units of buffered crystalline sodium penicillin-G. The one-dose vial is also available, if desired, with an accompanying ampoule of Water for Injection, B.P. Potency of the suspension is maintained for seven days at refrigerator temperatures.

PARKE, DAVIS & COMPANY

MEDICAMENTA VERA

the forms of

Fe++ ***Iron Therapy*** Fe+++

are varied

Ferrous Sulphate

OSTEOTABS WITH IRON AND VITAMIN C

Each enteric coated tablet contains:

Purified Selected Bone Meal	5 grains
Ferrous Sulphate U.S.P. Crystal	5 grains
Vitamin C (Ascorbic Acid)	25 mgms.
Vitamin A	500 Int. Units
Vitamin D	500 Int. Units
Vitamin B_1 (Thiamin HCI.)	0.75 mgm.
Vitamin B_2 (Riboflavin)	0.75 mgm.
Iodine	0.05 mgm.

Ferrous Gluconate

FERROSULPH NERVINE TABLETS

Each sugar coated tablet contains:

Ferrous sulphate U.S.P. Crystal	5 grains
Vitamin B_1 (Thiamin HCI.)	1.0 mgm.
Vitamin B_2 (Riboflavin)	0.5 mgm.
Phenobarbital Sodium	1/4 grain
Ext. Nux Vomica	1/4 grain
Phosphorus	1/100 grain

FERRANCA TABLETS

Each sugar coated tablet contains:

Ferrous Gluconate N.F.	5 grains
Vitamin B_1 (Thiamin HCI.)	1 mgm.
Vitamin B_2 (Riboflavin)	0.75 mgm.
Niacinamide	3.5 mgms.
Liver Extract	equivalent to 20 grains of fresh liver

Iron Pyrophosphate

IRO-PLEX SYRUP

Each ounce contains:

Iron Pyrophosphate	24 grains
Vitamin B_1 (Thiamin HCI.)	3.0 mgms.
Vitamin B_2 (Riboflavin)	4.0 mgm.
Vitamin B_6 (Pyridoxine)	1.5 mgm.
Pantothenic Acid	7.5 mgm.
Niacinamide	15.0 mgm.

ANGLO-CANADIAN DRUG COMPANY LTD.

OSHAWA CANADA

ANCA

THE SUFFIX ANCA WILL IDENTIFY ANY OF OUR PRODUCTS ON A PRESCRIPTION